27è Congrès National
et
8è Congrès Francophone
de réanimation

SOCIÉTÉ
DE RÉANIMATION
DE LANGUE FRANÇAISE

FAUT-IL TRAITER TOUTES LES HYPONATRÉMIES EN RÉANIMATION ?

Pr Ag Oussama JAOUED

Réanimation Médicale

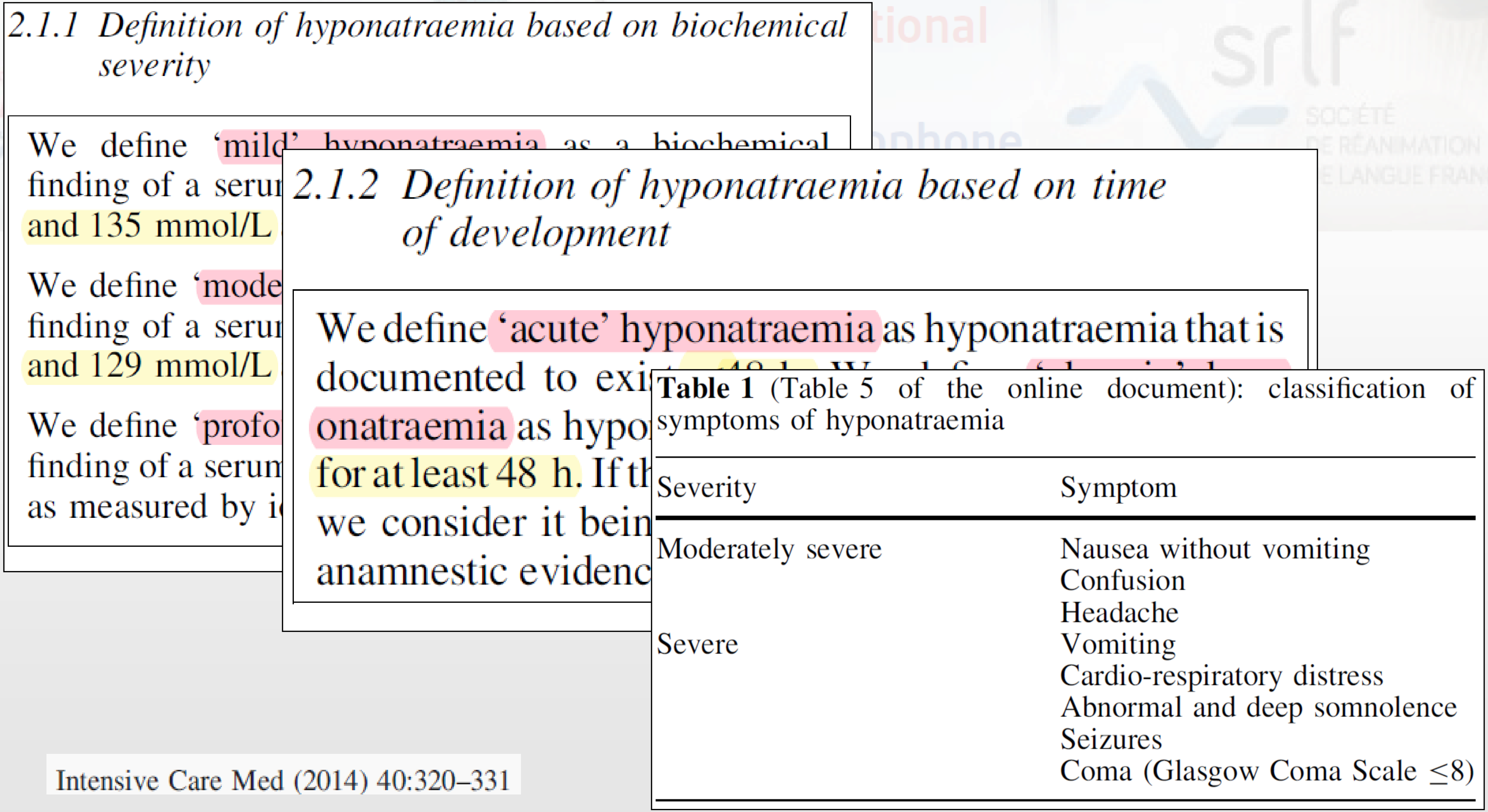
CHU Taher Sfar Mahdia

27e Congrès National
et
Congrès Francophone
de réanimation
srlf
SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE

Faut-il traiter toutes les hyponatrémies en réanimation ?

- Natrémie < 135mEq/L
- Trouble hydroélectrolytique le plus fréquent
- 20% des patients âgés de plus de 65 ans, 35% des hospitalisés, 30% des insuffisants cardiaques et 50% des patients avec une cirrhose ou cancer
- En réanimation, l’incidence des hyponatrémies varie de 10 à 45 % selon les études

Burst V. Etiology and epidemiology of hyponatremia. Front Horm Res. 2019;52:24-35



2.1.1 Definition of hyponatraemia based on biochemical severity

We define 'mild' hyponatraemia as a biochemical
finding of a serur
and 135 mmol/L

We define 'mode
finding of a serur
and 129 mmol/L

We define 'profo
finding of a serum
as measured by i

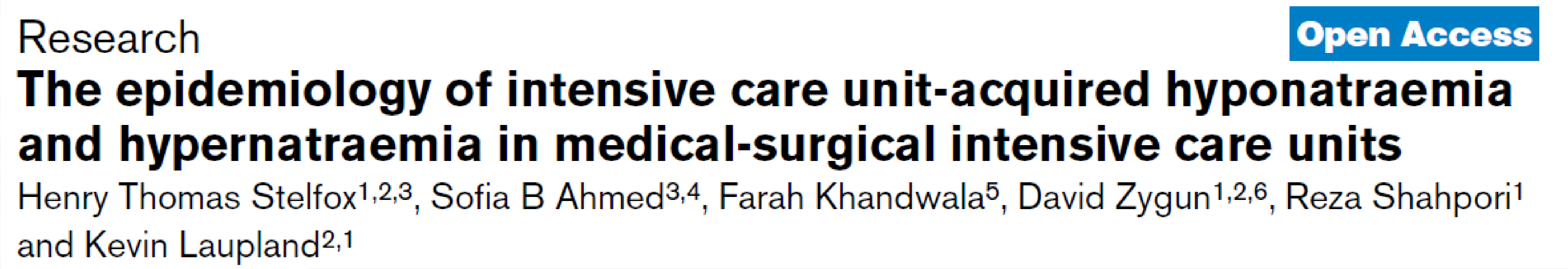
2.1.2 Definition of hyponatraemia based on time of development

We define 'acute' hyponatraemia as hyponatraemia that is
documented to exi
onatraemia as hypo
for at least 48 h. If th
we consider it bein
anamnestic evidenc

Table 1 (Table 5 of the online document): classification of symptoms of hyponatraemia

Severity	Symptom
Moderately severe	Nausea without vomiting Confusion Headache
Severe	Vomiting Cardio-respiratory distress Abnormal and deep somnolence Seizures Coma (Glasgow Coma Scale ≤8)

Intensive Care Med (2014) 40:320–331



Research

Open Access

The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units

Henry Thomas Stelfox[1,2,3], Sofia B Ahmed[3,4], Farah Khandwala[5], David Zygun[1,2,6], Reza Shahpori[1] and Kevin Laupland[2,1]

- 8142 pat
  d'hospital
- 917 (11
  hyponatre
- Hyponatr

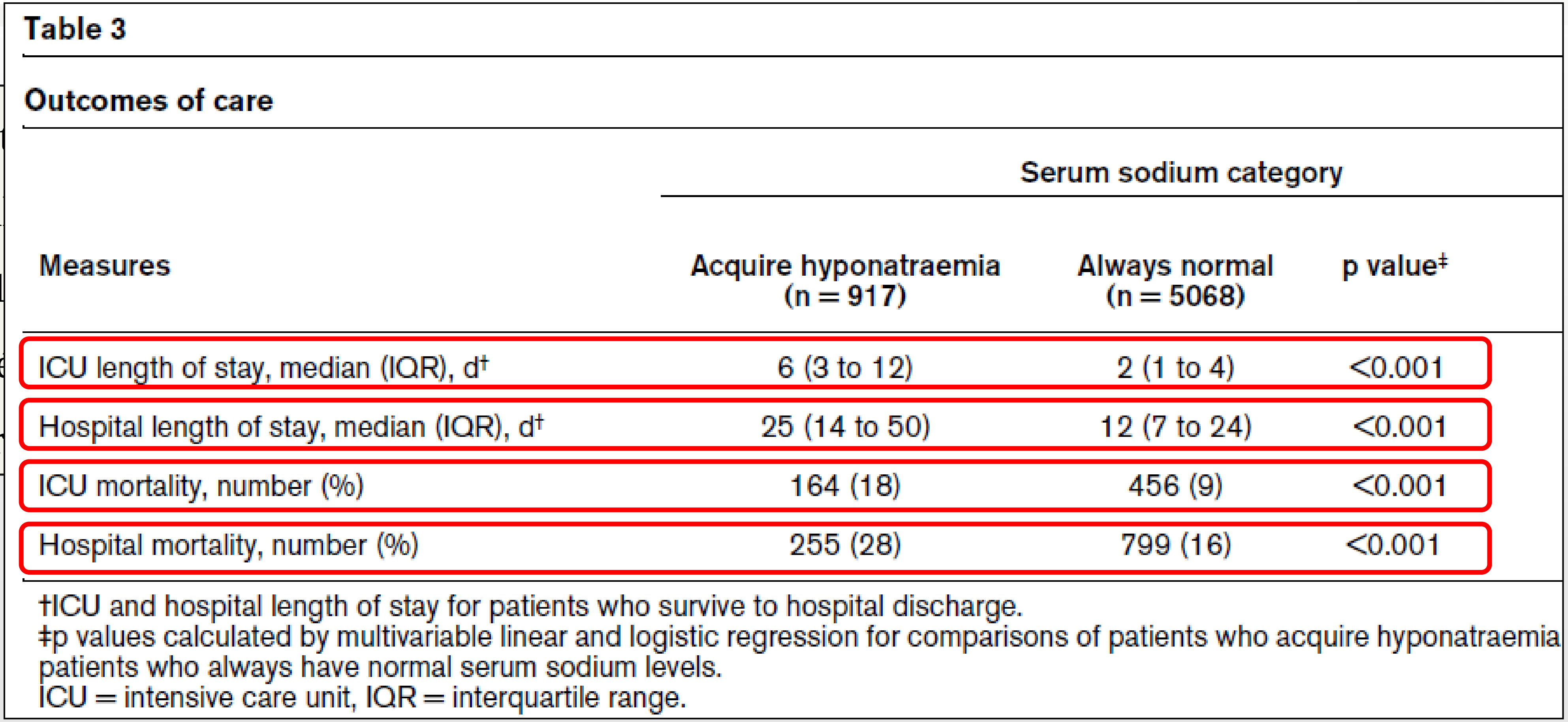


Table 3

Outcomes of care

Measures	Serum sodium category		
	Acquire hyponatraemia (n = 917)	Always normal (n = 5068)	p value‡
ICU length of stay, median (IQR), d†	6 (3 to 12)	2 (1 to 4)	<0.001
Hospital length of stay, median (IQR), d†	25 (14 to 50)	12 (7 to 24)	<0.001
ICU mortality, number (%)	164 (18)	456 (9)	<0.001
Hospital mortality, number (%)	255 (28)	799 (16)	<0.001

†ICU and hospital length of stay for patients who survive to hospital discharge.
‡p values calculated by multivariable linear and logistic regression for comparisons of patients who acquire hyponatraemia
patients who always have normal serum sodium levels.
ICU = intensive care unit, IQR = interquartile range.

Critical Care 2008, 12:R162 Stelfox et al.

Fluctuations in Serum Sodium Level Are Associated With an Increased Risk of Death in Surgical ICU Patients*

- Prévalence à l’admission : 11.1% (n = 1,215/9431)
- Prévalence de l’hyponatrémie acquise en réanimation : 13.6% (n = 1,483)

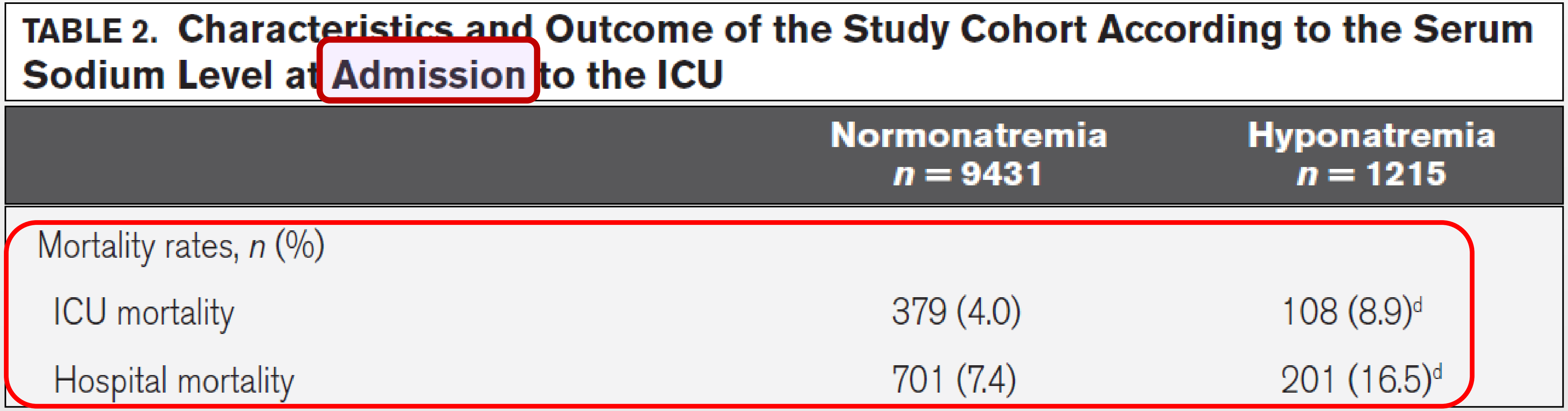


TABLE 2. Characteristics and Outcome of the Study Cohort According to the Serum Sodium Level at Admission to the ICU

	Normonatremia *n* = 9431	Hyponatremia *n* = 1215
Mortality rates, *n* (%)		
ICU mortality	379 (4.0)	108 (8.9)[d]
Hospital mortality	701 (7.4)	201 (16.5)[d]

Critical Care Medicine 41(1):p 133-142, January 2013

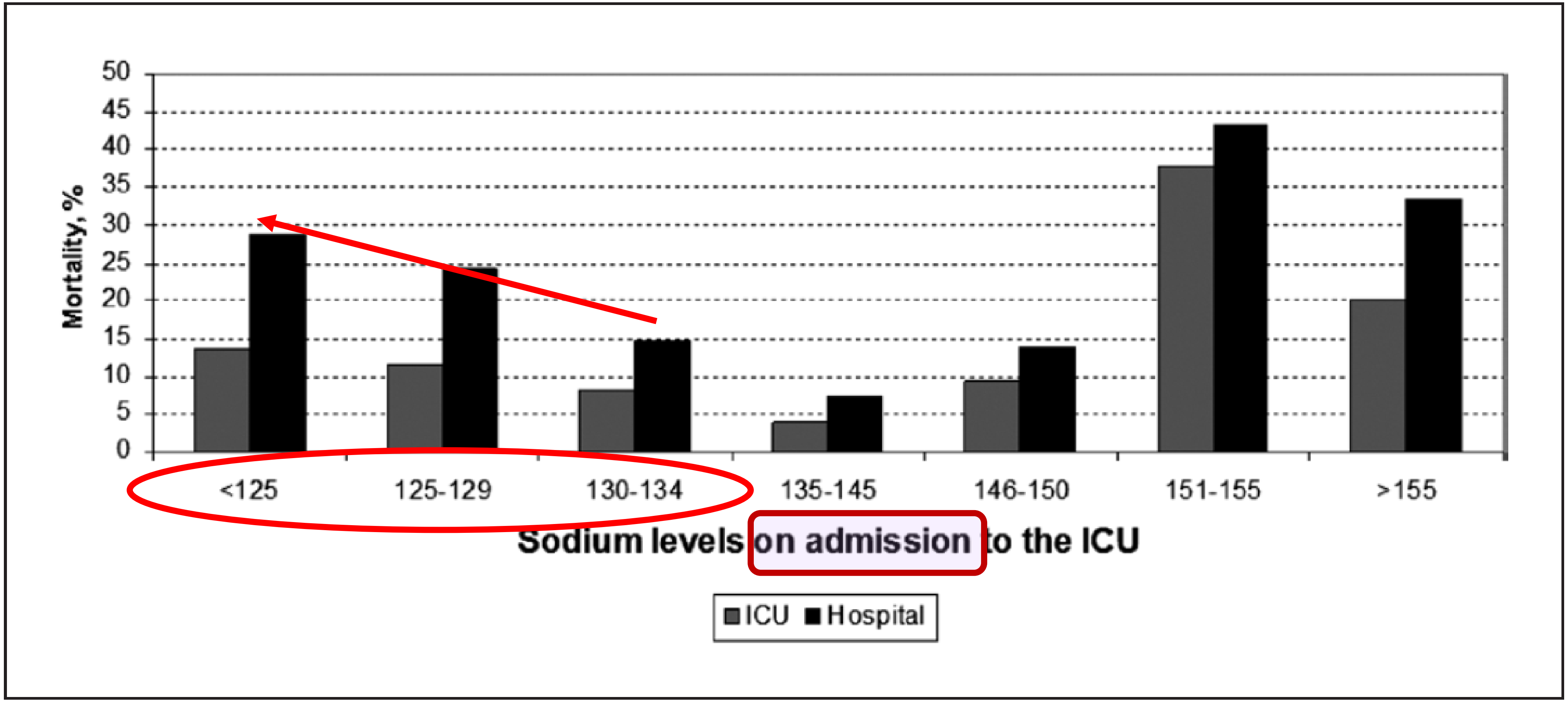


Figure 2. Bar chart representing ICU and hospital mortality rates according to sodium levels at admission to the ICU. $p < 0.01$ for ICU and hospital mortality among groups (Cochran–Armitage trend test).

Critical Care Medicine 41(1):p 133-142, January 2013

Fluctuations in Serum Sodium Level Are Associated With an Increased Risk of Death in Surgical ICU Patients*

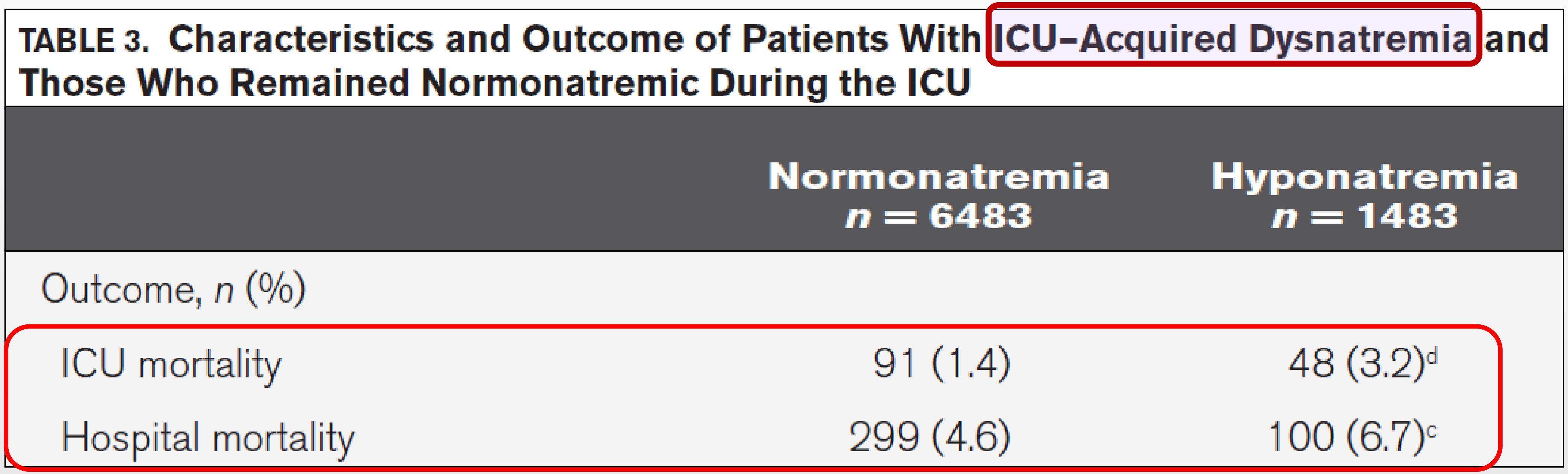


TABLE 3. **Characteristics and Outcome of Patients With ICU–Acquired Dysnatremia and Those Who Remained Normonatremic During the ICU**

	Normonatremia *n* = 6483	Hyponatremia *n* = 1483
Outcome, *n* (%)		
ICU mortality	91 (1.4)	48 (3.2)[d]
Hospital mortality	299 (4.6)	100 (6.7)[c]

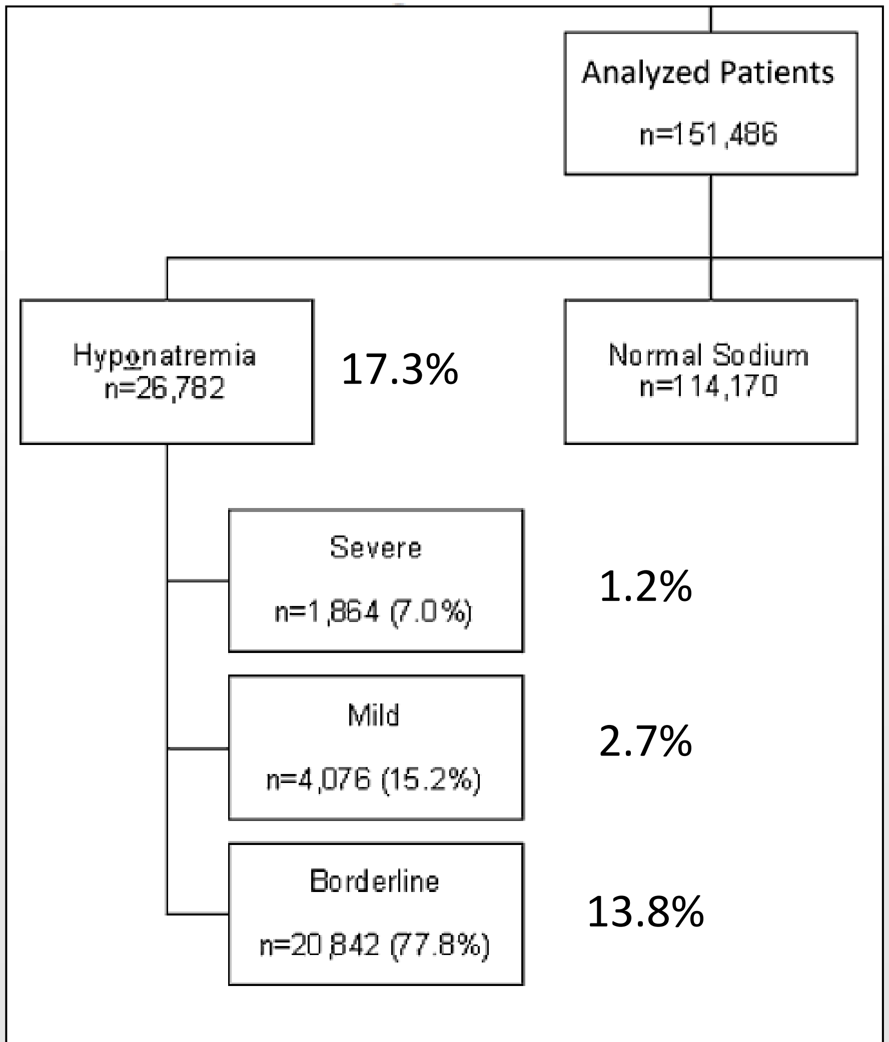
Critical Care Medicine 41(1):p 133-142, January 2013

Intensive Care Med (2010) 36:304–311
DOI 10.1007/s00134-009-1692-0

ORIGINAL

Georg-Christian Funk
Gregor Lindner
Wilfred Druml
Barbara Metnitz
Christoph Schwarz
Peter Bauer
Philipp G. H. Metnitz

Incidence and prognosis of dysnatremias



Analyzed Patients
n=151,486

Hyponatremia
n=26,782
17.3%

Normal Sodium
n=114,170

Severe
n=1,864 (7.0%)
1.2%

Mild
n=4,076 (15.2%)
2.7%

Borderline
n=20,842 (77.8%)
13.8%

Intensive Care Med (2010) 36:304–311

Table 1 Unadjusted associa stics

Characteristic	odium ,170)	*P*
Patients affected (%)		
Age (years), mean ± SD		<0.0001
Males (%)		<0.0001
Medical type of admission		<0.0001
Scheduled surgical type of a		<0.0001
Unscheduled surgical type o		<0.0001
Number of organ failures, n		<0.0001
Sodium-corrected SAPS II s	9)	<0.0001
Observed ICU mortality (%		<0.0001
Length of ICU stay, days, n		<0.0001
Observed hospital mortality		<0.0001

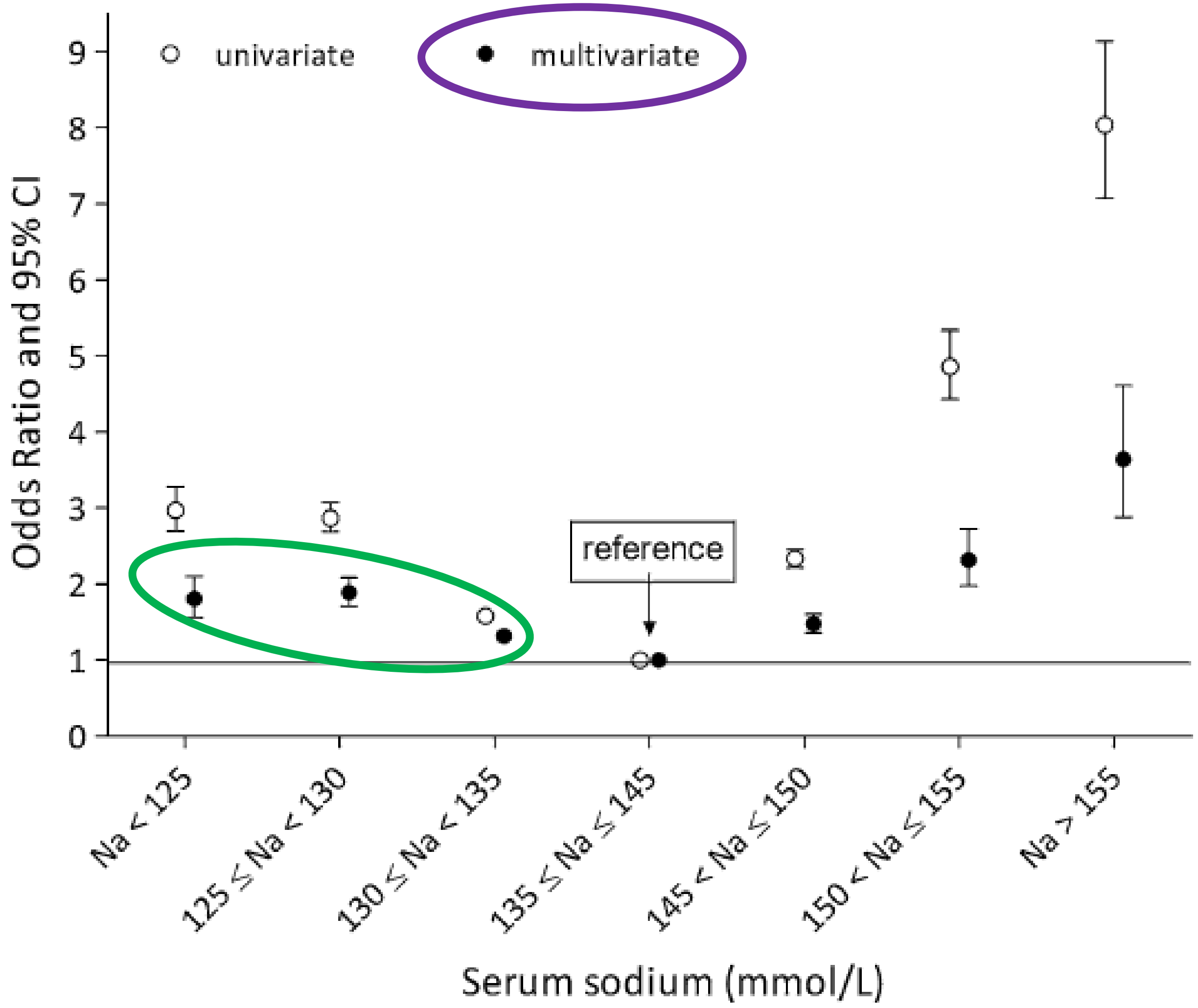


Fig. 2 Unadjusted (*open circles*) and adjusted (*filled circles*) risk of hospital mortality stratified by serum sodium on ICU admission. CI, confidence interval

Intensive Care Med (2010) 36:304–311

Hyponatremia in critically ill patients

Rajesh Padhi, Baikuntha Nath Panda, Snehalata Jag

- Etude prospective observationnelle
- 12 mois

- Groupe hyponatrémie (n=251) : 36%
- Hyponatremie à l'admission : 34%

- Hyponatrémie avec euvolémie : 148 (58.96%)
- Hyponatrémie avec hypervolémie : 66 (26.29%)
- Hyponatrémie avec hypovolémie : 37 (14.74%)

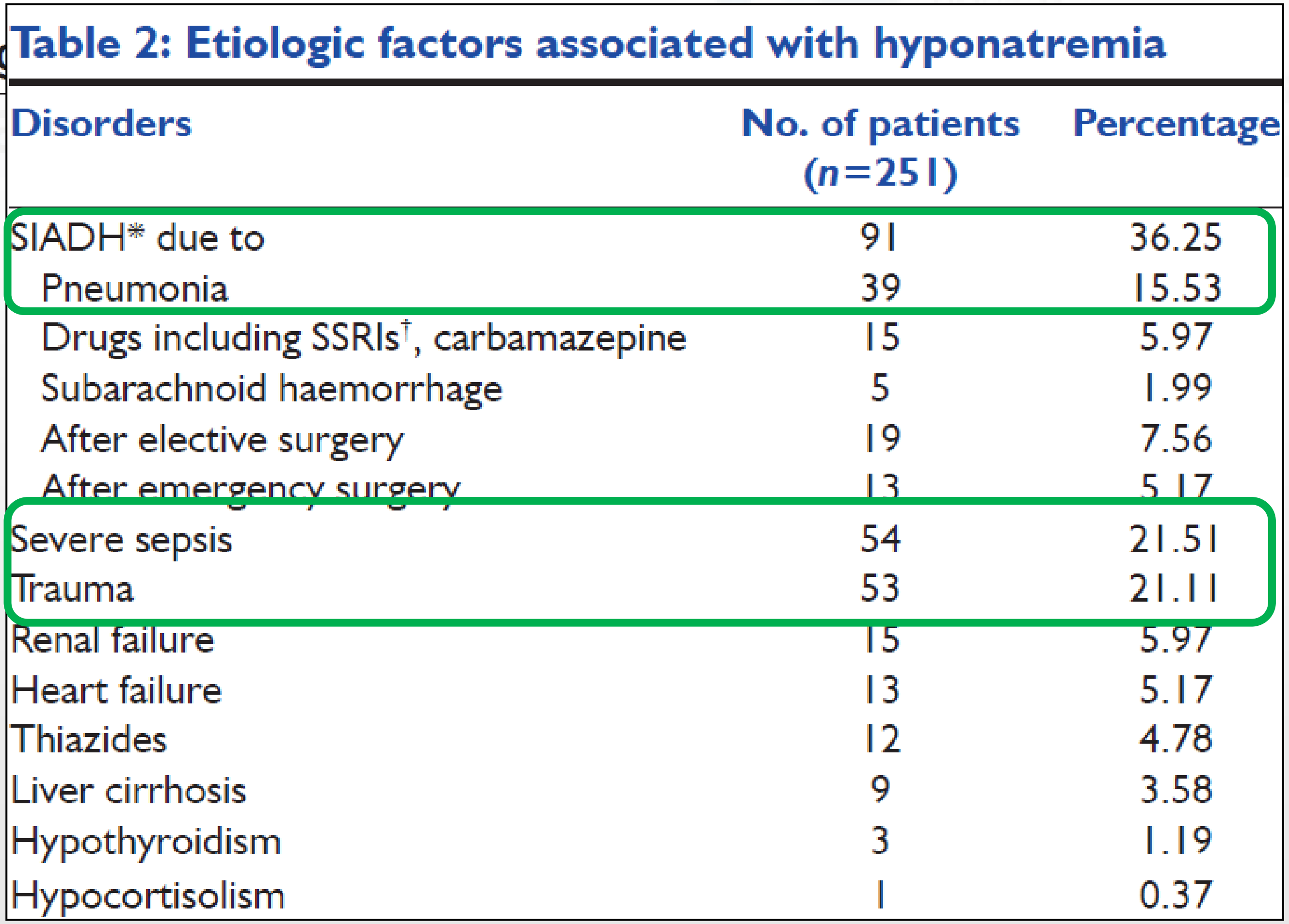


Table 2: Etiologic factors associated with hyponatremia

Disorders	No. of patients (*n*=251)	Percentage
SIADH* due to	91	36.25
Pneumonia	39	15.53
Drugs including SSRIs†, carbamazepine	15	5.97
Subarachnoid haemorrhage	5	1.99
After elective surgery	19	7.56
After emergency surgery	13	5.17
Severe sepsis	54	21.51
Trauma	53	21.11
Renal failure	15	5.97
Heart failure	13	5.17
Thiazides	12	4.78
Liver cirrhosis	9	3.58
Hypothyroidism	3	1.19
Hypocortisolism	1	0.37

Indian Journal of Critical Care Medicine ; February 2014

Hyponatremia in critically ill patients

Rajesh Padhi, Baikuntha Nath Panda, Snehalata Jagati, Subhas Chandra Patra[1]

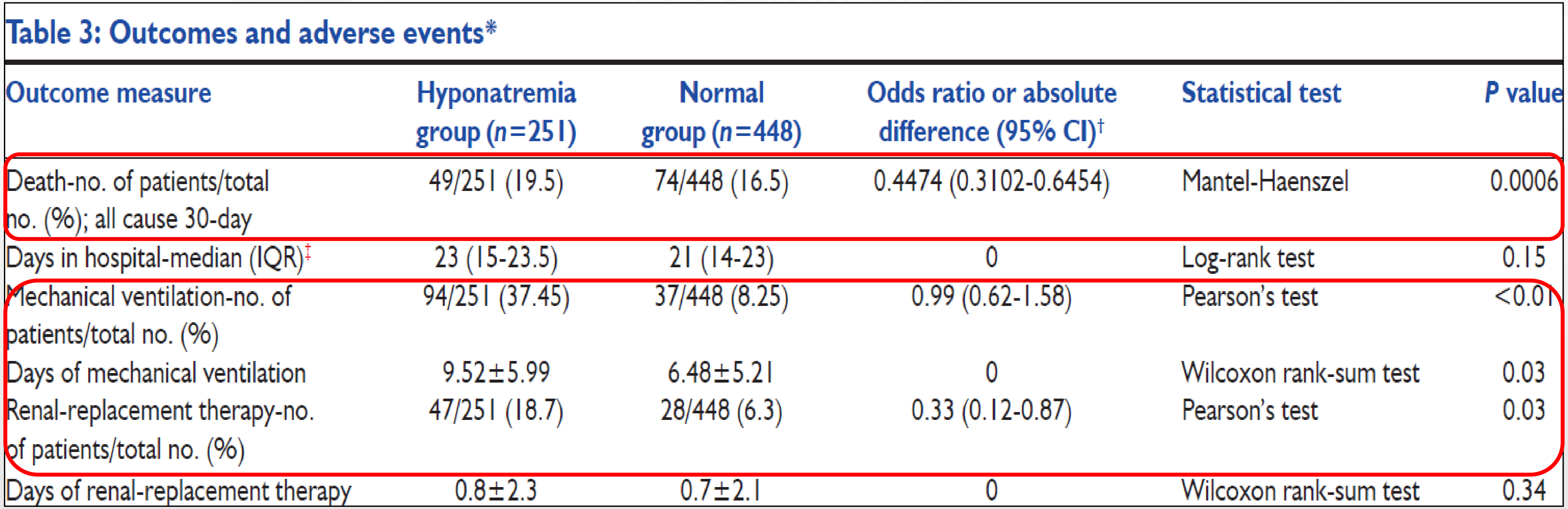


Table 3: Outcomes and adverse events*

Outcome measure	Hyponatremia group (n=251)	Normal group (n=448)	Odds ratio or absolute difference (95% CI)†	Statistical test	P value
Death-no. of patients/total no. (%); all cause 30-day	49/251 (19.5)	74/448 (16.5)	0.4474 (0.3102-0.6454)	Mantel-Haenszel	0.0006
Days in hospital-median (IQR)‡	23 (15-23.5)	21 (14-23)	0	Log-rank test	0.15
Mechanical ventilation-no. of patients/total no. (%)	94/251 (37.45)	37/448 (8.25)	0.99 (0.62-1.58)	Pearson's test	<0.01
Days of mechanical ventilation	9.52±5.99	6.48±5.21	0	Wilcoxon rank-sum test	0.03
Renal-replacement therapy-no. of patients/total no. (%)	47/251 (18.7)	28/448 (6.3)	0.33 (0.12-0.87)	Pearson's test	0.03
Days of renal-replacement therapy	0.8±2.3	0.7±2.1	0	Wilcoxon rank-sum test	0.34

Indian Journal of Critical Care Medicine ; February 2014

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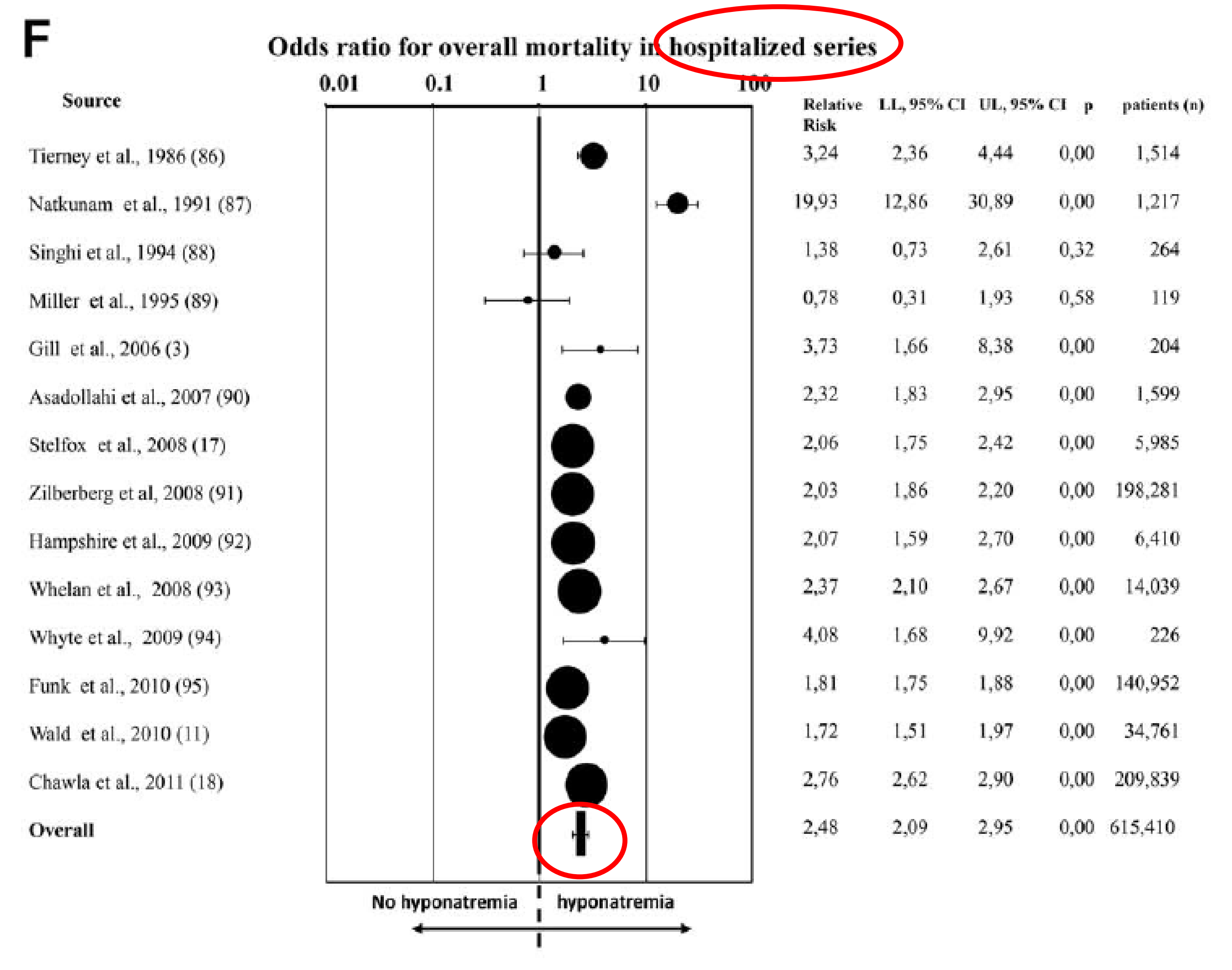
PLOS | ONE

Moderate Hyponatremia Is A
Risk of Mortality: Evidence f

850222 patients dont 147948 patients avec hyponatrémie
➔17,4% d'hyponatrémie

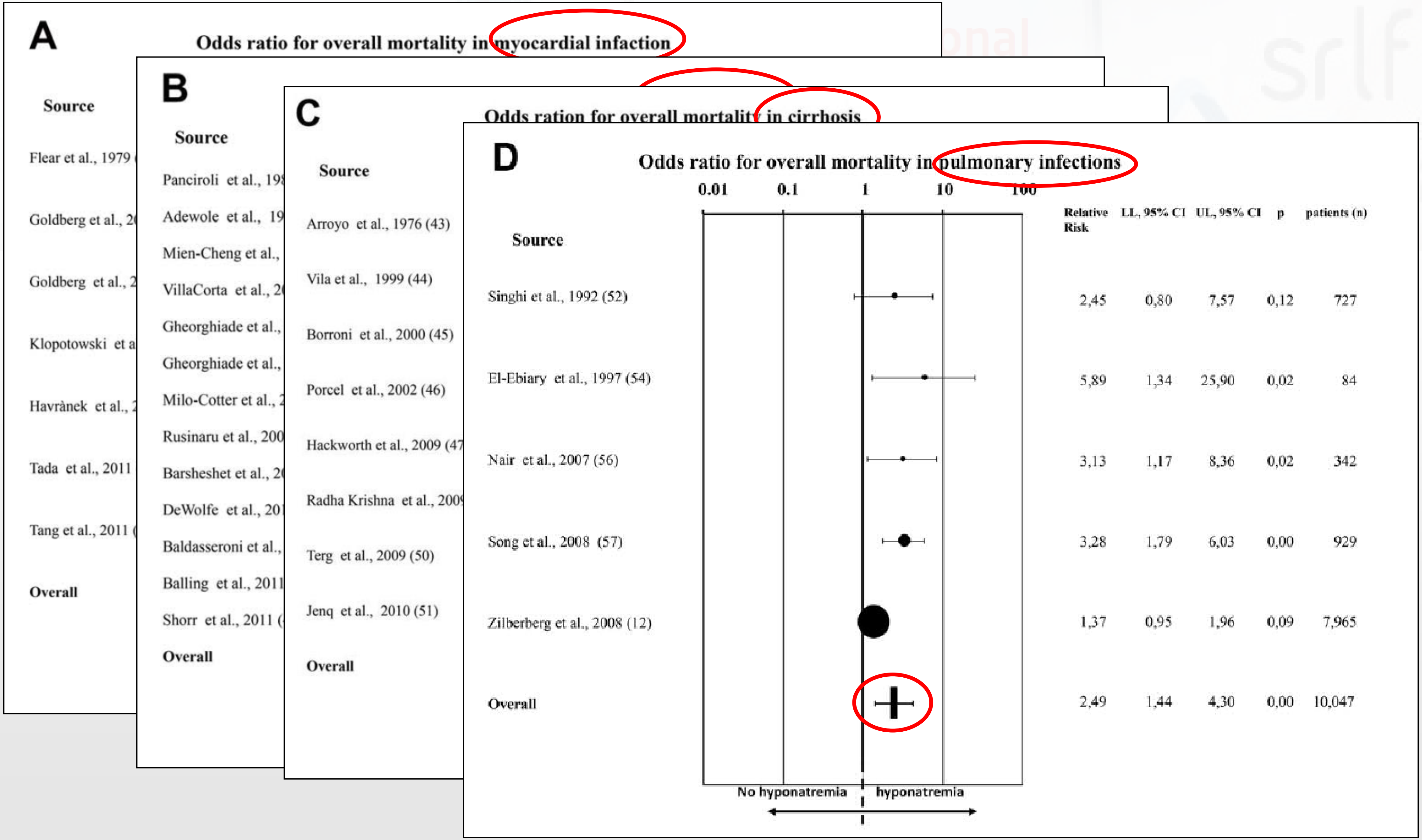
130.1±5.6 vs 134.9±5.1 mmol/L

Hyponatrémie était associée à la mortalité globale : RR = 2.60[2.31–2.93]; p= 0.0001



Source	Relative Risk	LL, 95% CI	UL, 95% CI	p	patients (n)
Tierney et al., 1986 (86)	3,24	2,36	4,44	0,00	1,514
Natkunam et al., 1991 (87)	19,93	12,86	30,89	0,00	1,217
Singhi et al., 1994 (88)	1,38	0,73	2,61	0,32	264
Miller et al., 1995 (89)	0,78	0,31	1,93	0,58	119
Gill et al., 2006 (3)	3,73	1,66	8,38	0,00	204
Asadollahi et al., 2007 (90)	2,32	1,83	2,95	0,00	1,599
Stelfox et al., 2008 (17)	2,06	1,75	2,42	0,00	5,985
Zilberberg et al, 2008 (91)	2,03	1,86	2,20	0,00	198,281
Hampshire et al., 2009 (92)	2,07	1,59	2,70	0,00	6,410
Whelan et al., 2008 (93)	2,37	2,10	2,67	0,00	14,039
Whyte et al., 2009 (94)	4,08	1,68	9,92	0,00	226
Funk et al., 2010 (95)	1,81	1,75	1,88	0,00	140,952
Wald et al., 2010 (11)	1,72	1,51	1,97	0,00	34,761
Chawla et al., 2011 (18)	2,76	2,62	2,90	0,00	209,839
Overall	2,48	2,09	2,95	0,00	615,410

PLoS ONE 8(12): e80451 2013



A

Odds ratio for overall mortality in myocardial infaction

Source

Flear et al., 1979 (

Goldberg et al., 2

Goldberg et al., 2

Klopotowski et a

Havrànek et al., 2

Tada et al., 2011

Tang et al., 2011 (

Overall

B

Source

Panciroli et al., 19

Adewole et al., 19

Mien-Cheng et al.,

VillaCorta et al., 2

Gheorghiade et al.,

Gheorghiade et al.,

Milo-Cotter et al., 2

Rusinaru et al., 200

Barsheshet et al., 2

DeWolfe et al., 20

Baldasseroni et al.,

Balling et al., 2011

Shorr et al., 2011 (

Overall

C

Odds ration for overall mortality in cirrhosis

Source

Arroyo et al., 1976 (43)

Vila et al., 1999 (44)

Borroni et al., 2000 (45)

Porcel et al., 2002 (46)

Hackworth et al., 2009 (47

Radha Krishna et al., 200

Terg et al., 2009 (50)

Jenq et al., 2010 (51)

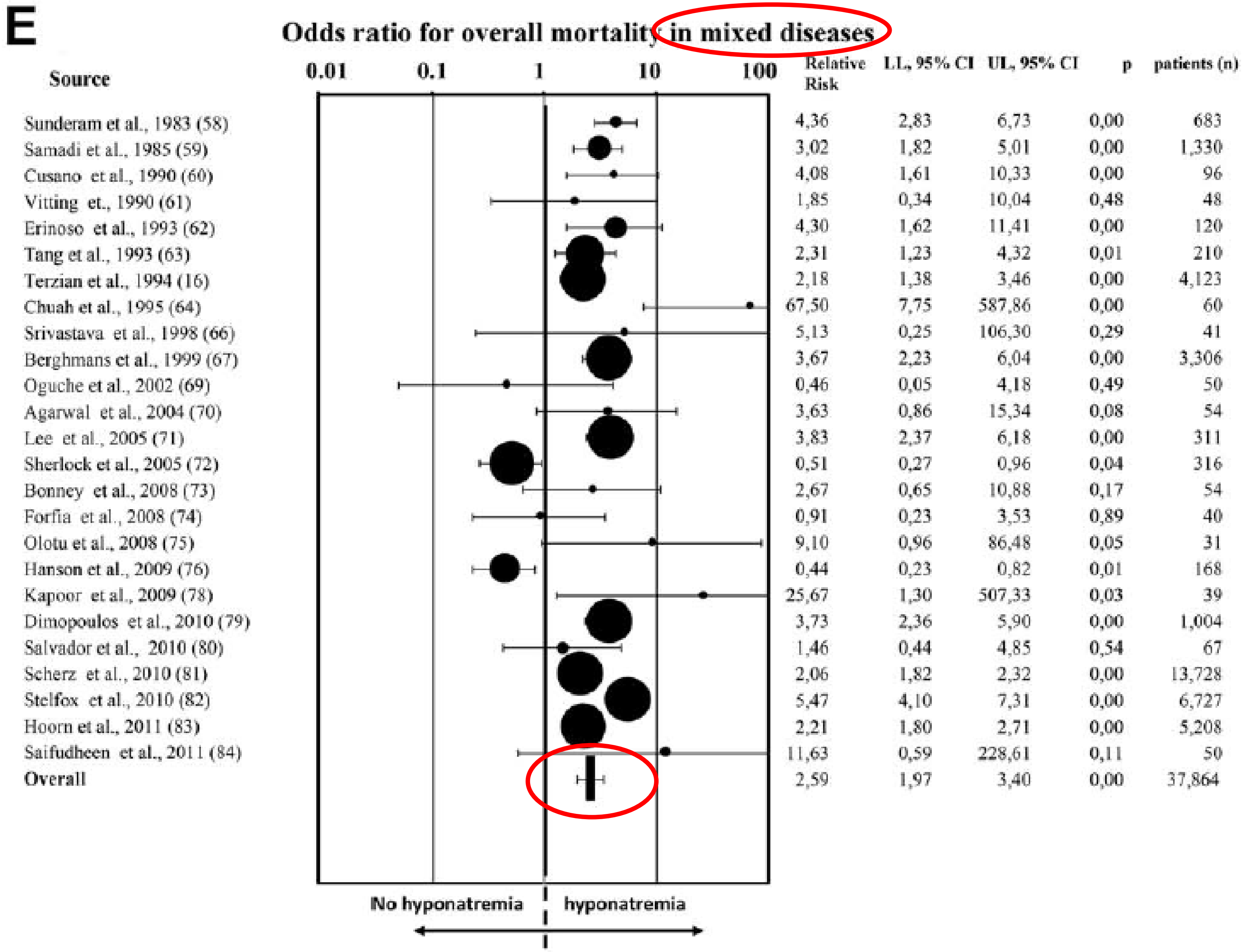
Overall

D

Odds ratio for overall mortality in pulmonary infections

Source	Relative Risk	LL, 95% CI	UL, 95% CI	p	patients (n)
Singhi et al., 1992 (52)	2,45	0,80	7,57	0,12	727
El-Ebiary et al., 1997 (54)	5,89	1,34	25,90	0,02	84
Nair et al., 2007 (56)	3,13	1,17	8,36	0,02	342
Song et al., 2008 (57)	3,28	1,79	6,03	0,00	929
Zilberberg et al., 2008 (12)	1,37	0,95	1,96	0,09	7,965
Overall	2,49	1,44	4,30	0,00	10,047

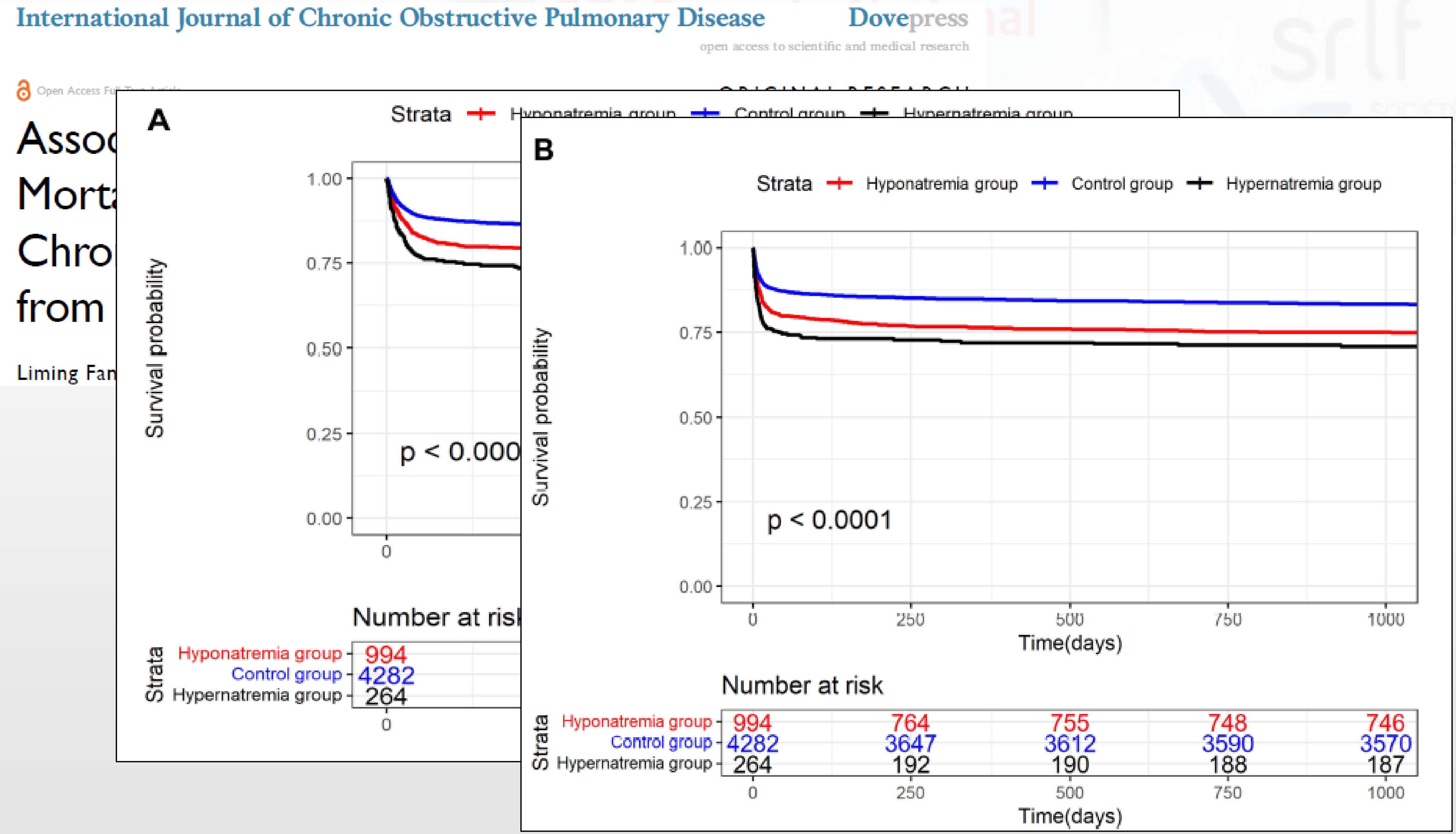
PLoS ONE 8(12): e80451 2013



Odds ratio for overall mortality in mixed diseases

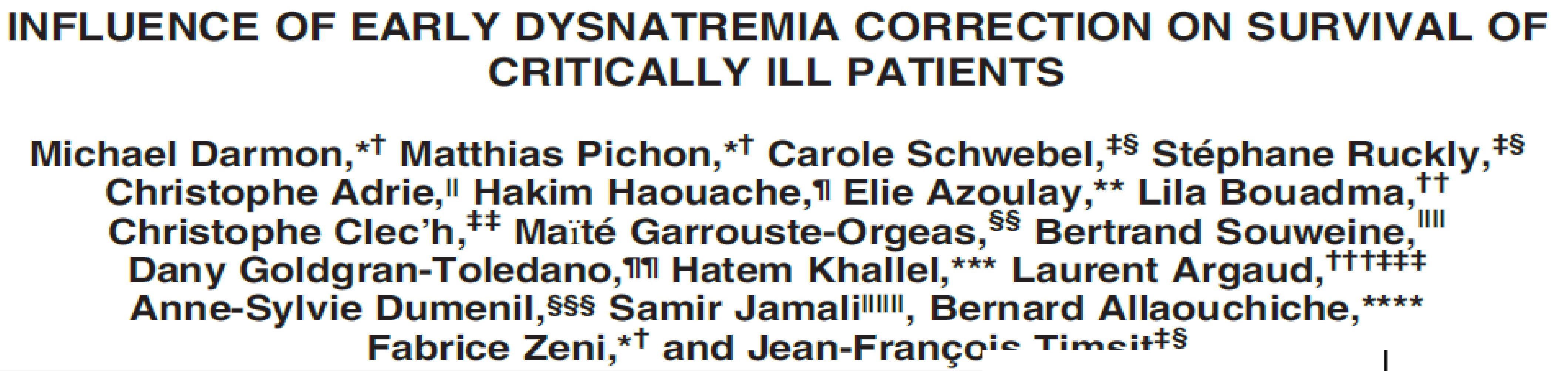
Source	Relative Risk	LL, 95% CI	UL, 95% CI	p	patients (n)
Sunderam et al., 1983 (58)	4,36	2,83	6,73	0,00	683
Samadi et al., 1985 (59)	3,02	1,82	5,01	0,00	1,330
Cusano et al., 1990 (60)	4,08	1,61	10,33	0,00	96
Vitting et., 1990 (61)	1,85	0,34	10,04	0,48	48
Erinoso et al., 1993 (62)	4,30	1,62	11,41	0,00	120
Tang et al., 1993 (63)	2,31	1,23	4,32	0,01	210
Terzian et al., 1994 (16)	2,18	1,38	3,46	0,00	4,123
Chuah et al., 1995 (64)	67,50	7,75	587,86	0,00	60
Srivastava et al., 1998 (66)	5,13	0,25	106,30	0,29	41
Berghmans et al., 1999 (67)	3,67	2,23	6,04	0,00	3,306
Oguche et al., 2002 (69)	0,46	0,05	4,18	0,49	50
Agarwal et al., 2004 (70)	3,63	0,86	15,34	0,08	54
Lee et al., 2005 (71)	3,83	2,37	6,18	0,00	311
Sherlock et al., 2005 (72)	0,51	0,27	0,96	0,04	316
Bonney et al., 2008 (73)	2,67	0,65	10,88	0,17	54
Forfia et al., 2008 (74)	0,91	0,23	3,53	0,89	40
Olotu et al., 2008 (75)	9,10	0,96	86,48	0,05	31
Hanson et al., 2009 (76)	0,44	0,23	0,82	0,01	168
Kapoor et al., 2009 (78)	25,67	1,30	507,33	0,03	39
Dimopoulos et al., 2010 (79)	3,73	2,36	5,90	0,00	1,004
Salvador et al., 2010 (80)	1,46	0,44	4,85	0,54	67
Scherz et al., 2010 (81)	2,06	1,82	2,32	0,00	13,728
Stelfox et al., 2010 (82)	5,47	4,10	7,31	0,00	6,727
Hoorn et al., 2011 (83)	2,21	1,80	2,71	0,00	5,208
Saifudheen et al., 2011 (84)	11,63	0,59	228,61	0,11	50
Overall	2,59	1,97	3,40	0,00	37,864

PLoS ONE 8(12): e80451 2013



Strata	0	250	500	750	1000
Hyponatremia group	994	764	755	748	746
Control group	4282	3647	3612	3590	3570
Hypernatremia group	264	192	190	188	187

International Journal of Chronic Obstructive Pulmonary Disease 2022:17 1143–1155



INFLUENCE OF EARLY DYSNATREMIA CORRECTION ON SURVIVAL OF CRITICALLY ILL PATIENTS

Michael Darmon,[*†] Matthias Pichon,[*†] Carole Schwebel,[‡§] Stéphane Ruckly,[‡§]
Christophe Adrie,[‖] Hakim Haouache,[¶] Elie Azoulay,[**] Lila Bouadma,[††]
Christophe Clec'h,[‡‡] Maïté Garrouste-Orgeas,[§§] Bertrand Souweine,[‖‖]
Dany Goldgran-Toledano,[¶¶] Hatem Khallel,[***] Laurent Argaud,[†††‡‡‡]
Anne-Sylvie Dumenil,[§§§] Samir Jamali[‖‖‖], Bernard Allaouchiche,[****]
Fabrice Zeni,[*†] and Jean-François Timsit[‡§]

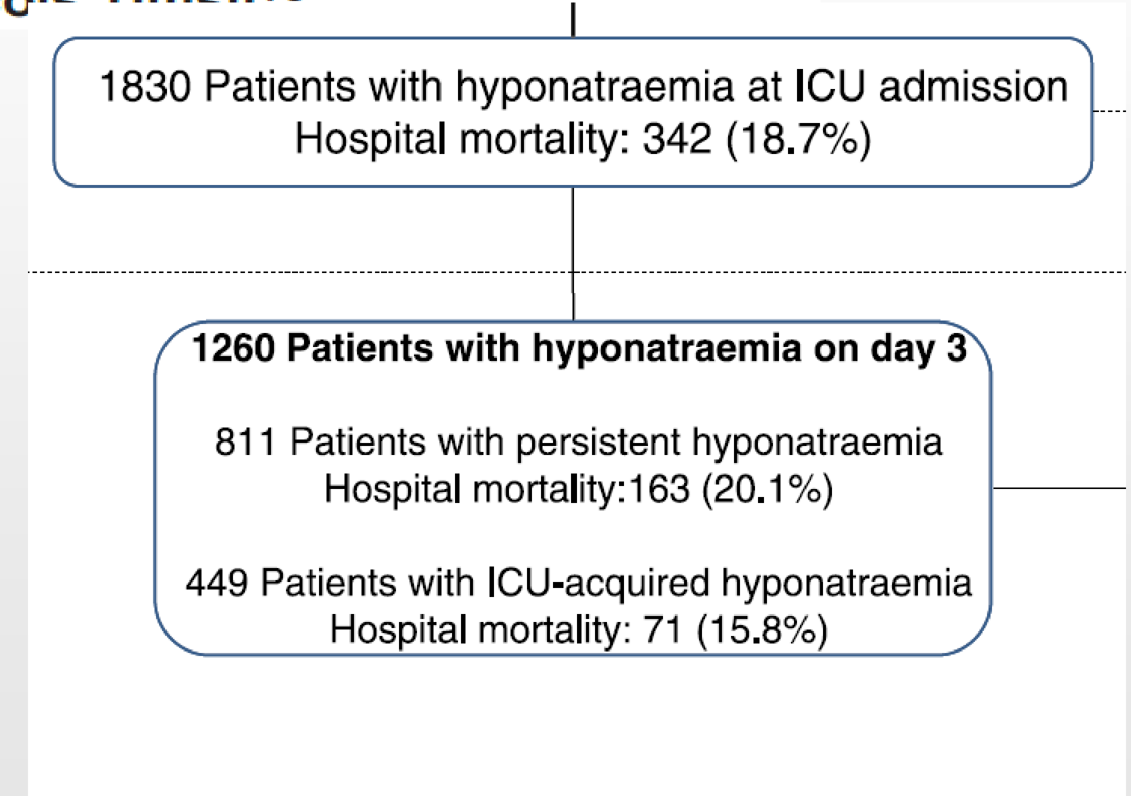
Etude observationnelle

18 réanimations

Impact de la dysnatrémie sur la mortalité à j 28

A j01, 1,830 patients (25.9%) avaient une hyponatrémie :

- 1,187 patients (16.8%) d'hyponatrémie minime
- 435 patients (6.2%) d'hyponatrémie modérée
- 208 patients (2.9) d'hyponatrémie sévère

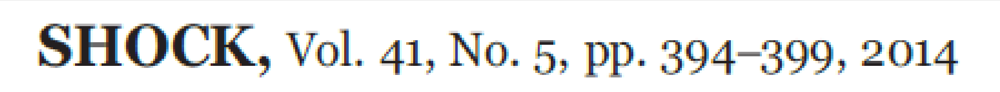


1830 Patients with hyponatraemia at ICU admission
Hospital mortality: 342 (18.7%)

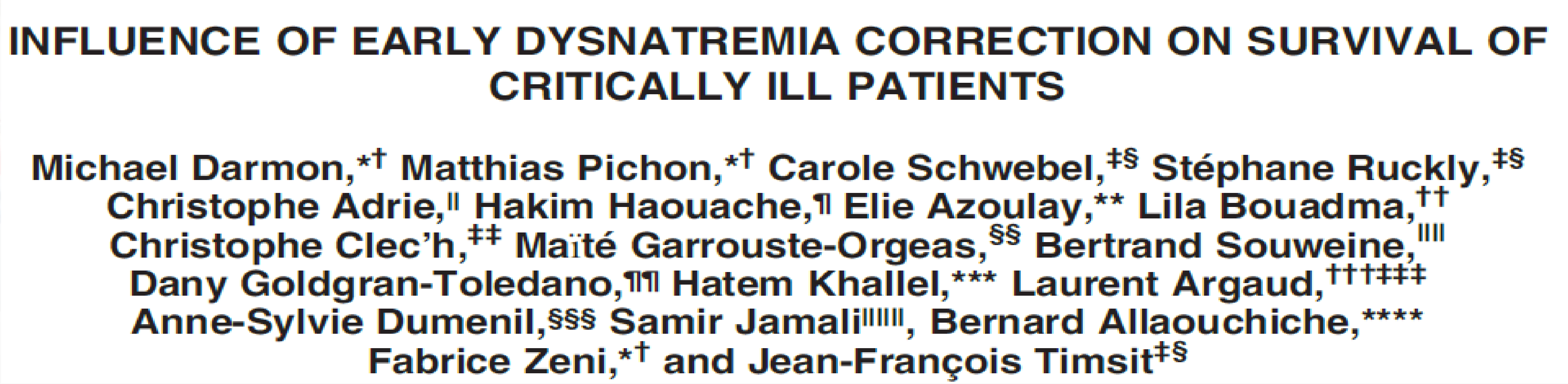
1260 Patients with hyponatraemia on day 3

811 Patients with persistent hyponatraemia
Hospital mortality:163 (20.1%)

449 Patients with ICU-acquired hyponatraemia
Hospital mortality: 71 (15.8%)



SHOCK, Vol. 41, No. 5, pp. 394–399, 2014



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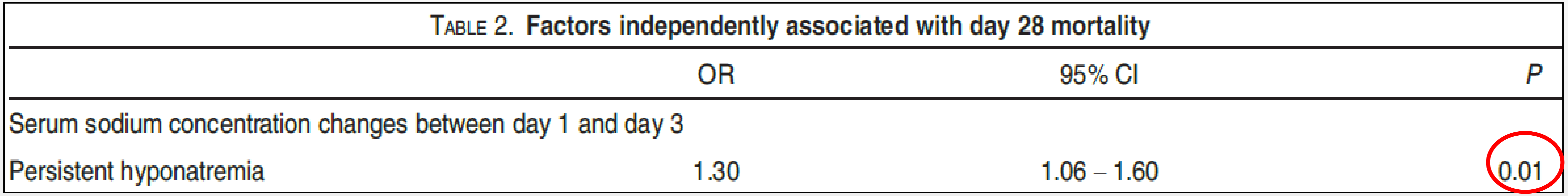


TABLE 2. Factors independently associated with day 28 mortality

	OR	95% CI	*P*
Serum sodium concentration changes between day 1 and day 3			
Persistent hyponatremia	1.30	1.06 – 1.60	0.01

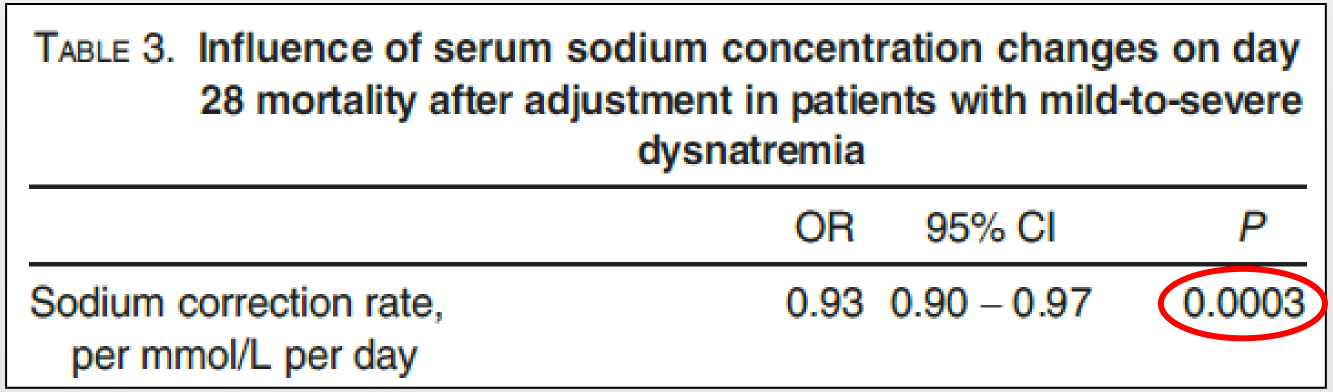
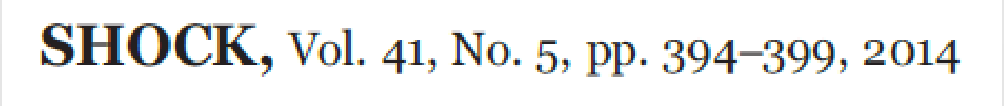
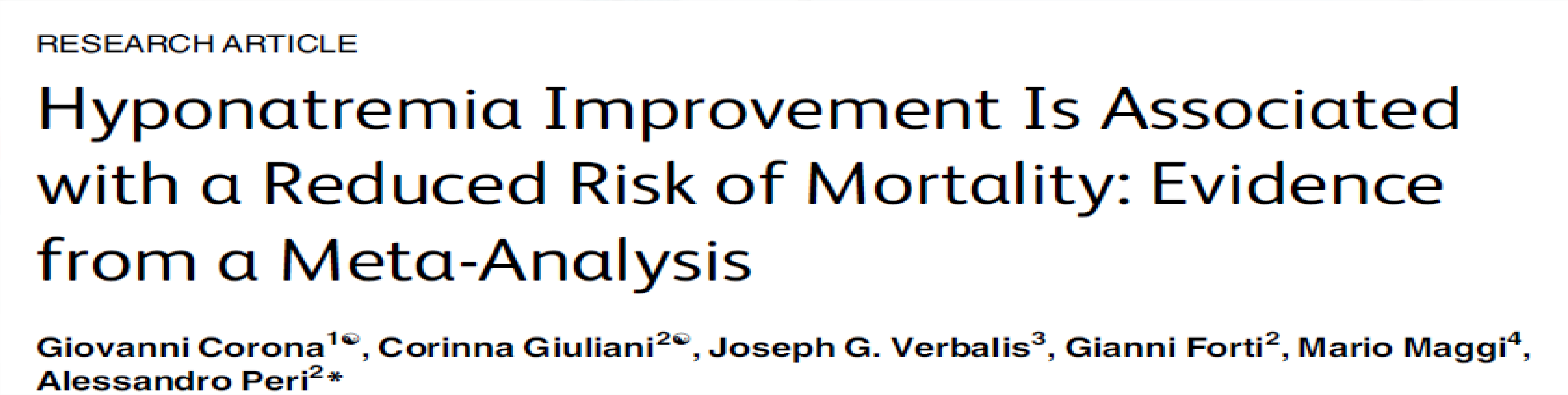


TABLE 3. Influence of serum sodium concentration changes on day 28 mortality after adjustment in patients with mild-to-severe dysnatremia

	OR	95% CI	*P*
Sodium correction rate, per mmol/L per day	0.93	0.90 – 0.97	0.0003



SHOCK, Vol. 41, No. 5, pp. 394–399, 2014



RESEARCH ARTICLE

PLOS | ONE

Hyponatremia Improvement Is Associated with a Reduced Risk of Mortality: Evidence from a Meta-Analysis

Giovanni Corona[1]☯, Corinna Giuliani[2]☯, Joseph G. Verbalis[3], Gianni Forti[2], Mario Maggi[4], Alessandro Peri[2]*

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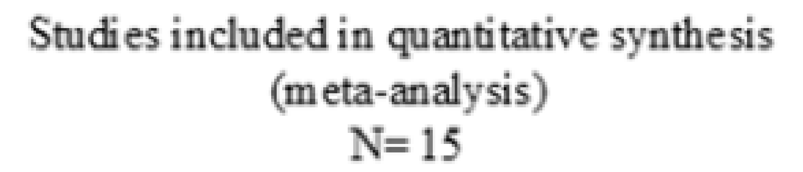

Studies included in quantitative synthesis
(meta-analysis)
N= 15

PLOS ONE | DOI:10.1371/journal.pone.0124105 April 23, 2015

RESEARCH ARTICLE

Hyponatremia Improvement Is Associated with a Reduced Risk of Mortality: Evidence from a Met

Giovanni Corona[1]☯, Co
Alessandro Peri[2]*

PLOS | ONE

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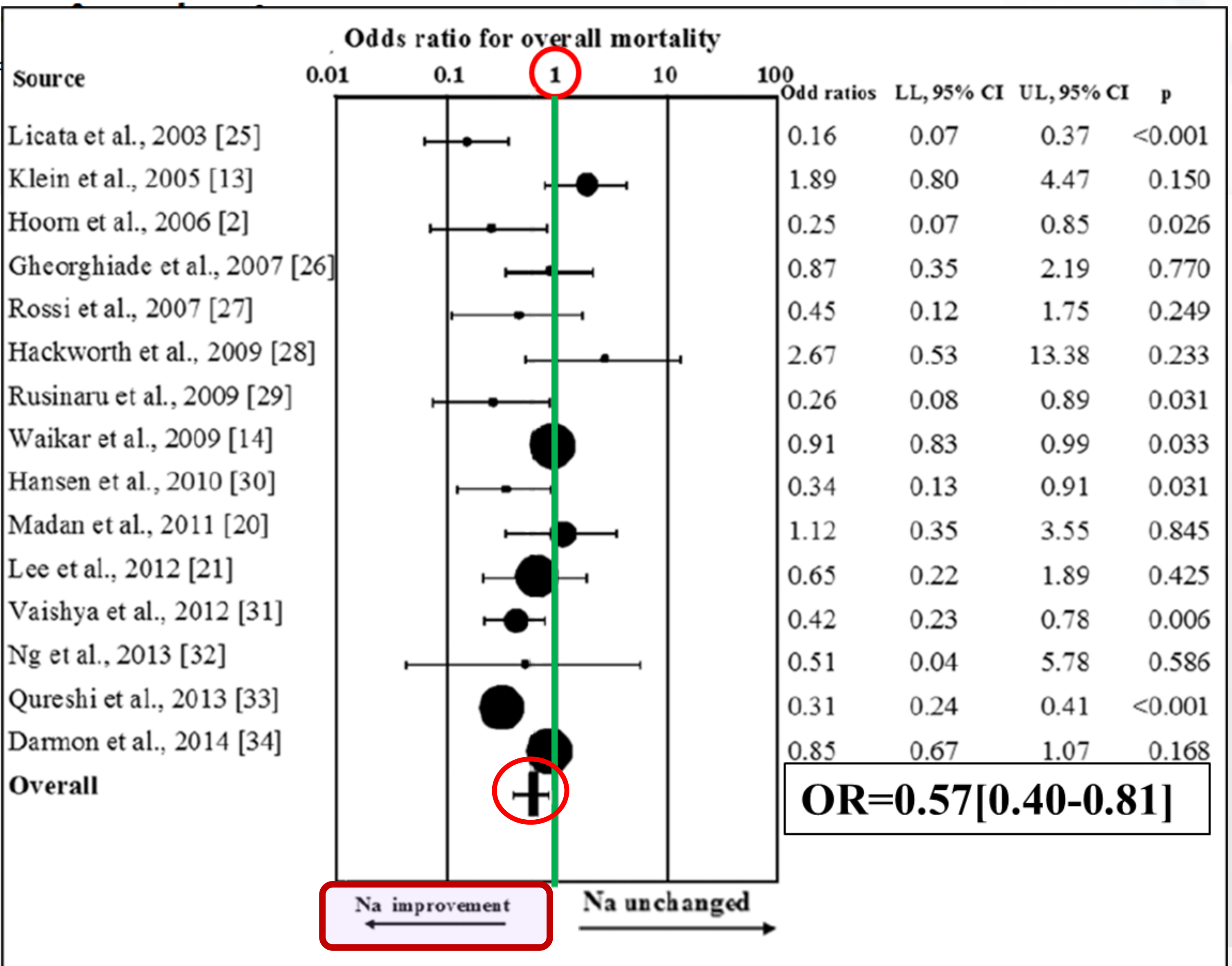
DE RÉANIMATION
DE LANGUE FRANÇAISE



Source	Odd ratios	LL, 95% CI	UL, 95% CI	p
Licata et al., 2003 [25]	0.16	0.07	0.37	<0.001
Klein et al., 2005 [13]	1.89	0.80	4.47	0.150
Hoorn et al., 2006 [2]	0.25	0.07	0.85	0.026
Gheorghiade et al., 2007 [26]	0.87	0.35	2.19	0.770
Rossi et al., 2007 [27]	0.45	0.12	1.75	0.249
Hackworth et al., 2009 [28]	2.67	0.53	13.38	0.233
Rusinaru et al., 2009 [29]	0.26	0.08	0.89	0.031
Waikar et al., 2009 [14]	0.91	0.83	0.99	0.033
Hansen et al., 2010 [30]	0.34	0.13	0.91	0.031
Madan et al., 2011 [20]	1.12	0.35	3.55	0.845
Lee et al., 2012 [21]	0.65	0.22	1.89	0.425
Vaishya et al., 2012 [31]	0.42	0.23	0.78	0.006
Ng et al., 2013 [32]	0.51	0.04	5.78	0.586
Qureshi et al., 2013 [33]	0.31	0.24	0.41	<0.001
Darmon et al., 2014 [34]	0.85	0.67	1.07	0.168
Overall				

OR=0.57[0.40-0.81]

Fig 3. Odds ratio for overall mortality rate in patients with any increase of serum [Na$^+$].

RESEARCH ARTICLE

Hyponatremia Improvement Is Associated with a Reduced Risk of Mortality: Evidence from a Meta-Analysis

Giovanni
Alessandr

PLOS | ONE

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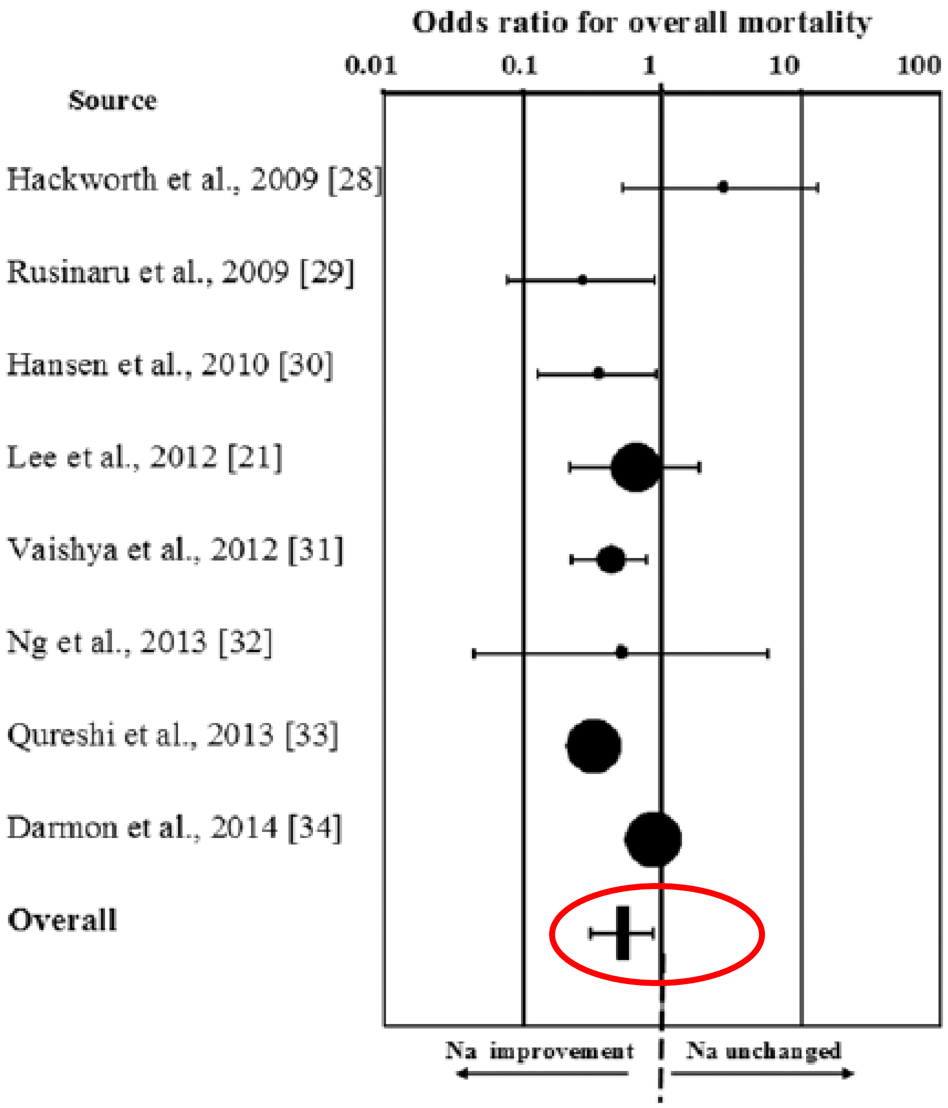

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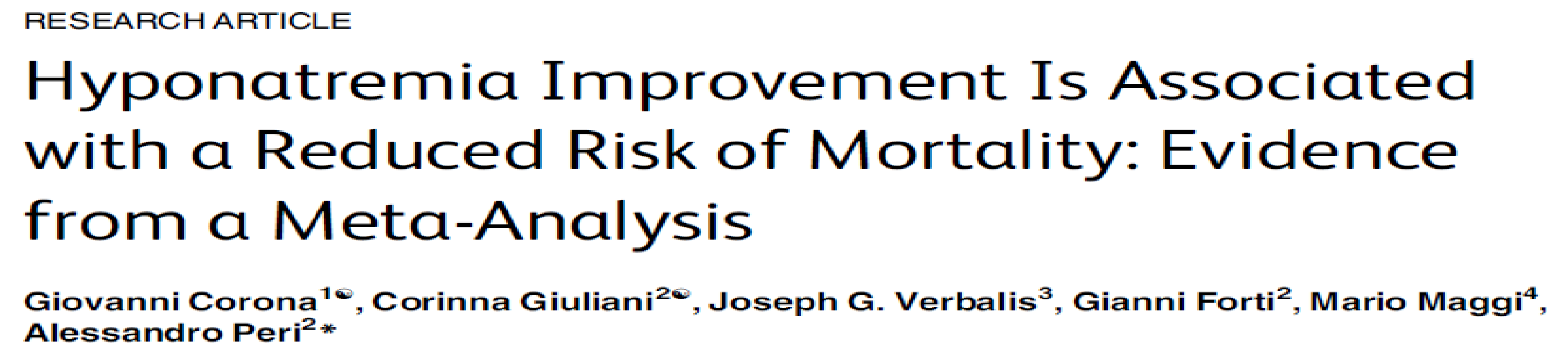
Darmon et al., 2014 [34]	0.85	0.67	1.07	0.168
Overall				

OR=0.51[0.31-0.86]

Fig 4. Odds ratio for overall mortality rate in patients from studies in which a threshold for serum [Na$^+$] improvement >130 mmol/L

- **08 études avec un seuil de correction > 130 mmol/l**

urnal.pone.0124105 April 23, 2015


RESEARCH ARTICLE

Hyponatremia Improvement Is Associated with a Reduced Risk of Mortality: Evidence from a Meta-Analysis

Giovanni Corona[1☯], Corinna Giuliani[2☯], Joseph G. Verbalis[3], Gianni Forti[2], Mario Maggi[4], Alessandro Peri[2*]

SOCIÉTÉ
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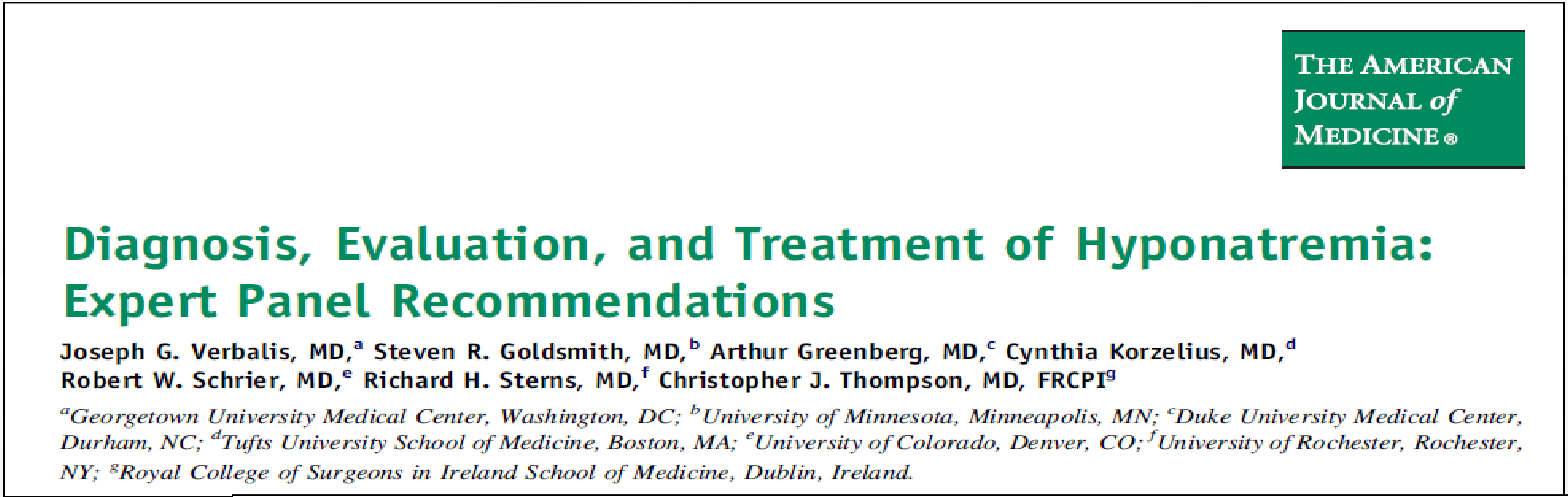
- **L’effet de l’amélioration de la natrémie sur la mortalité était plus évident :**
  - Sujets âgés
  - Patient avec une natrémie plus basse à l’inclusion

PLOS ONE | DOI:10.1371/journal.pone.0124105 April 23, 2015

Faut-il traiter toutes les hyponatrémies en réanimation ?

OUI

COMMENT?

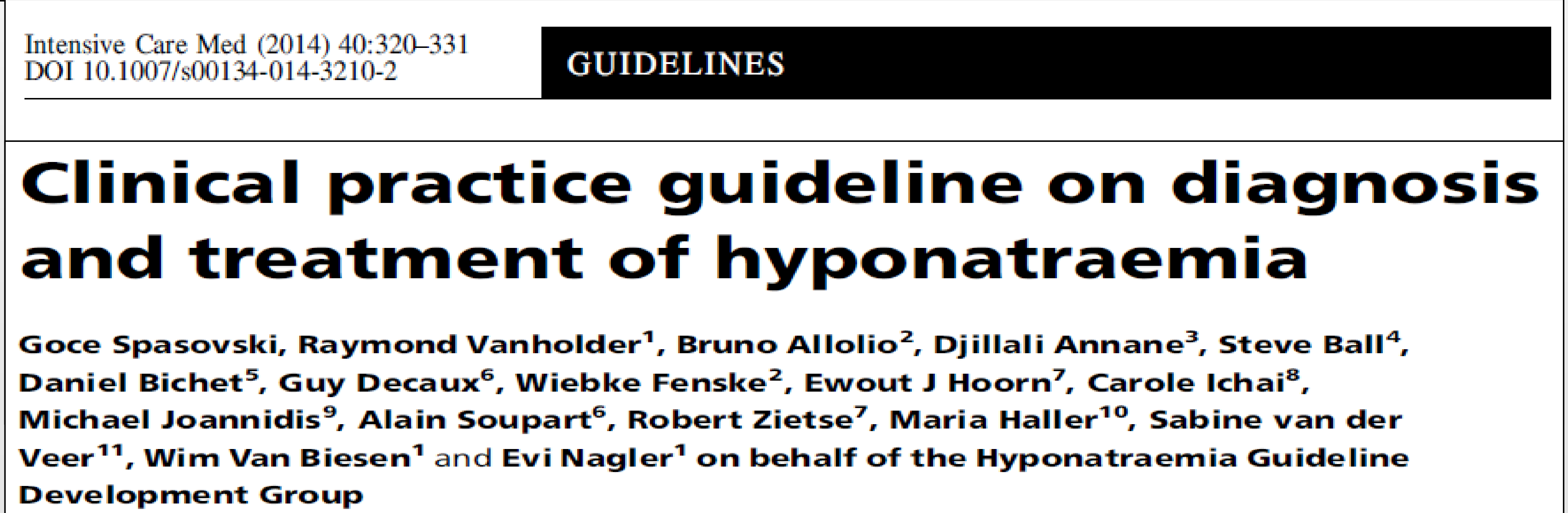


THE AMERICAN JOURNAL *of* MEDICINE®

Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations

Joseph G. Verbalis, MD,[a] Steven R. Goldsmith, MD,[b] Arthur Greenberg, MD,[c] Cynthia Korzelius, MD,[d] Robert W. Schrier, MD,[e] Richard H. Sterns, MD,[f] Christopher J. Thompson, MD, FRCPI[g]

[a]Georgetown University Medical Center, Washington, DC; [b]University of Minnesota, Minneapolis, MN; [c]Duke University Medical Center, Durham, NC; [d]Tufts University School of Medicine, Boston, MA; [e]University of Colorado, Denver, CO; [f]University of Rochester, Rochester, NY; [g]Royal College of Surgeons in Ireland School of Medicine, Dublin, Ireland.

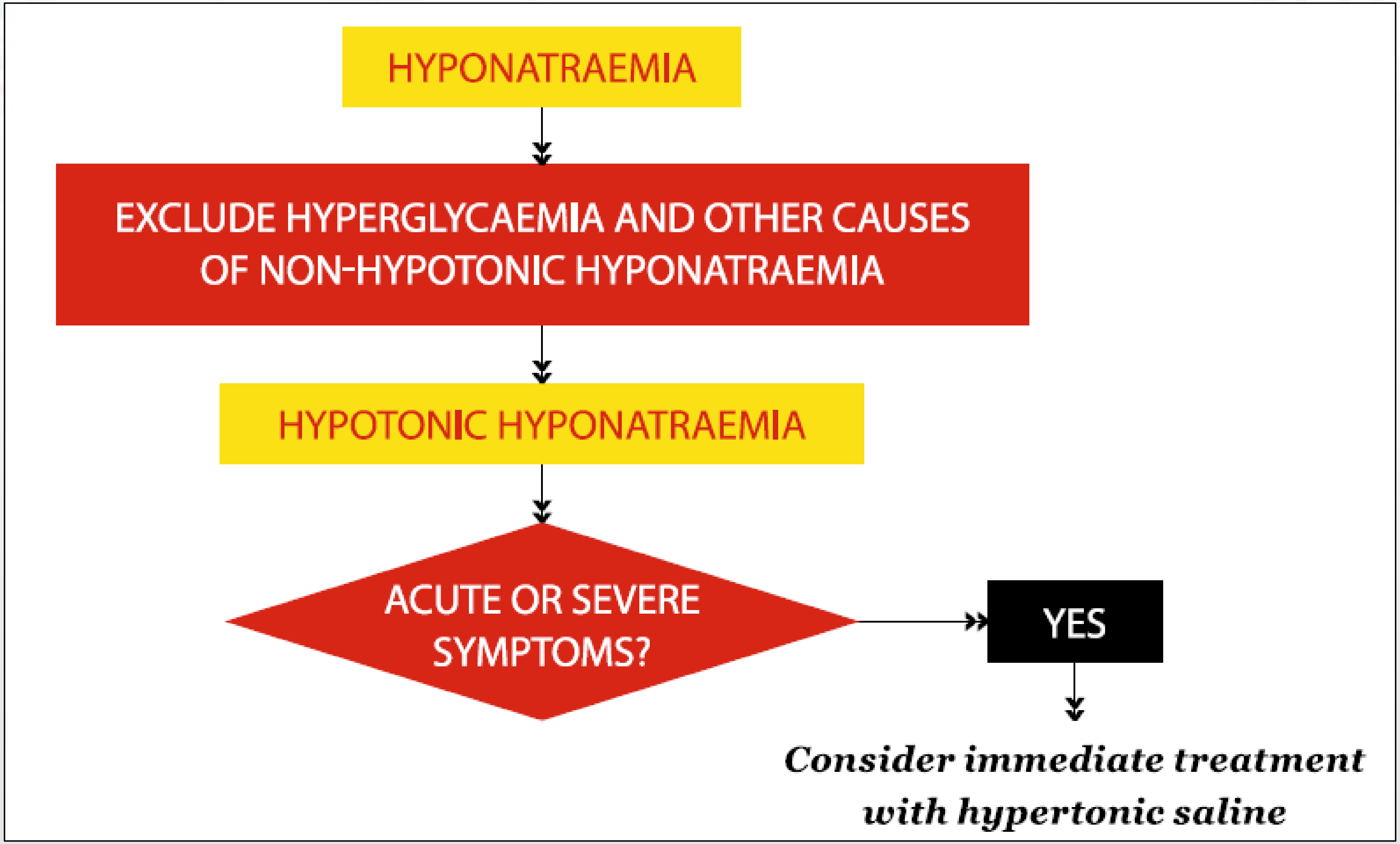


Intensive Care Med (2014) 40:320–331
DOI 10.1007/s00134-014-3210-2

GUIDELINES

Clinical practice guideline on diagnosis and treatment of hyponatraemia

Goce Spasovski, Raymond Vanholder[1], Bruno Allolio[2], Djillali Annane[3], Steve Ball[4], Daniel Bichet[5], Guy Decaux[6], Wiebke Fenske[2], Ewout J Hoorn[7], Carole Ichai[8], Michael Joannidis[9], Alain Soupart[6], Robert Zietse[7], Maria Haller[10], Sabine van der Veer[11], Wim Van Biesen[1] and **Evi Nagler[1] on behalf of the Hyponatraemia Guideline Development Group**



HYPONATRAEMIA

EXCLUDE HYPERGLYCAEMIA AND OTHER CAUSES OF NON-HYPOTONIC HYPONATRAEMIA

HYPOTONIC HYPONATRAEMIA

ACUTE OR SEVERE SYMPTOMS?

YES

Consider immediate treatment with hypertonic saline

Intensive Care Med (2014) 40:320–331

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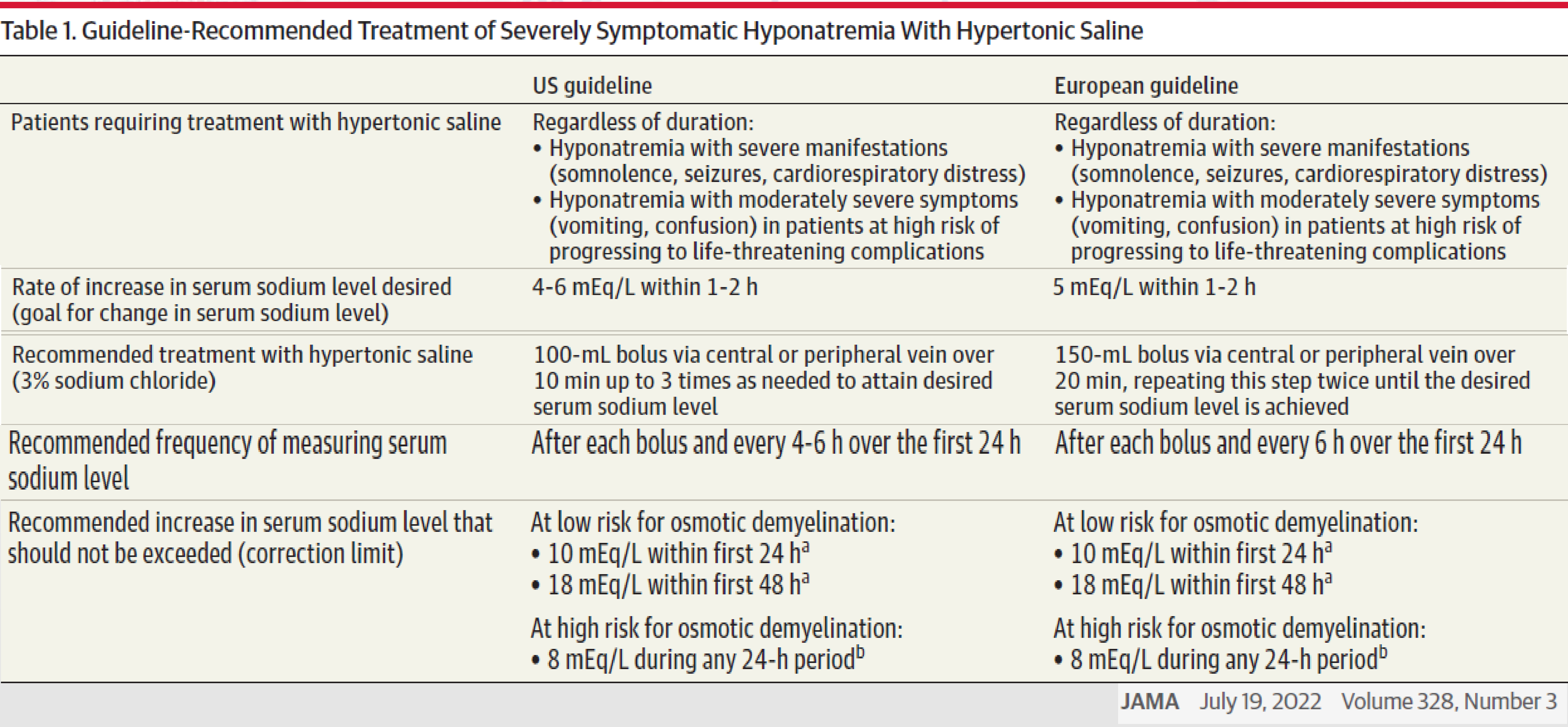
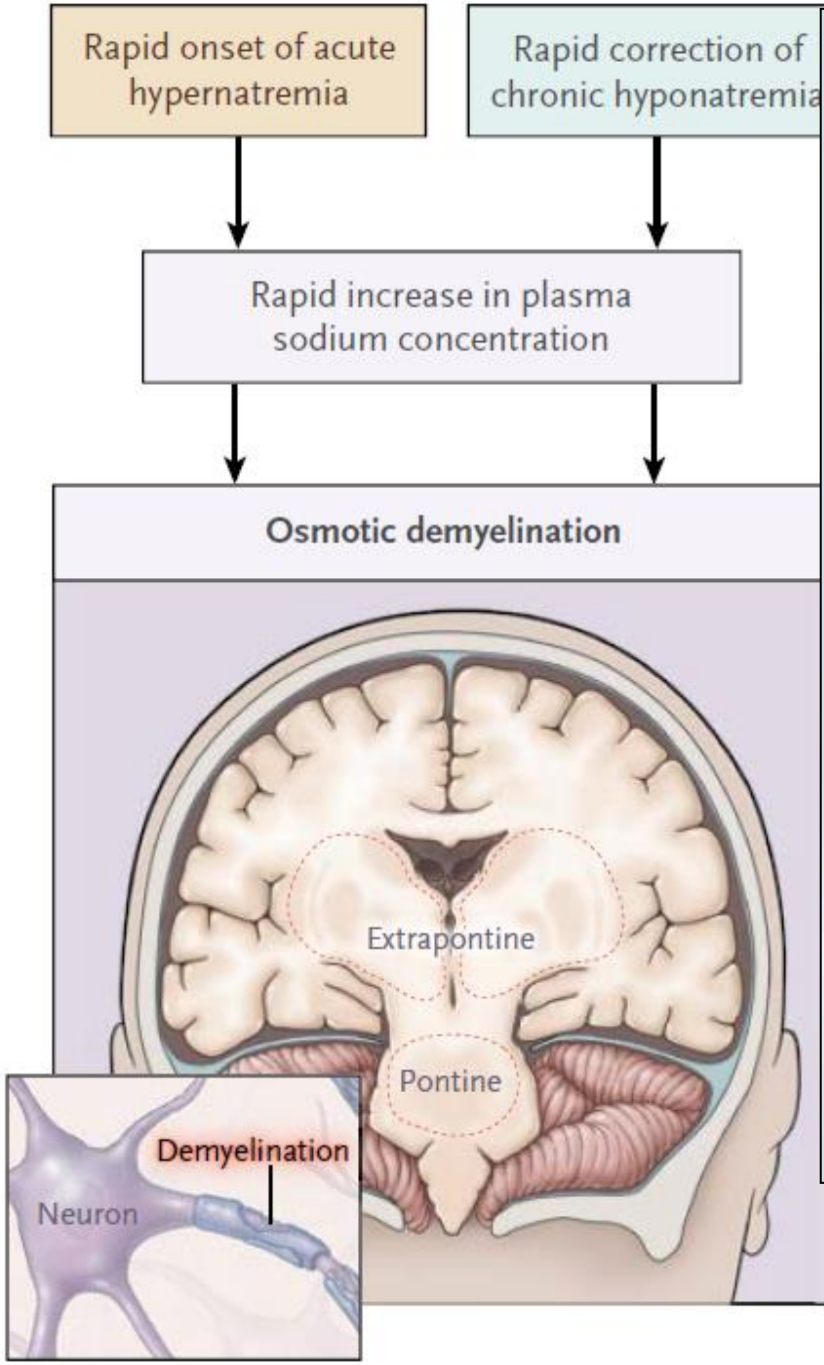
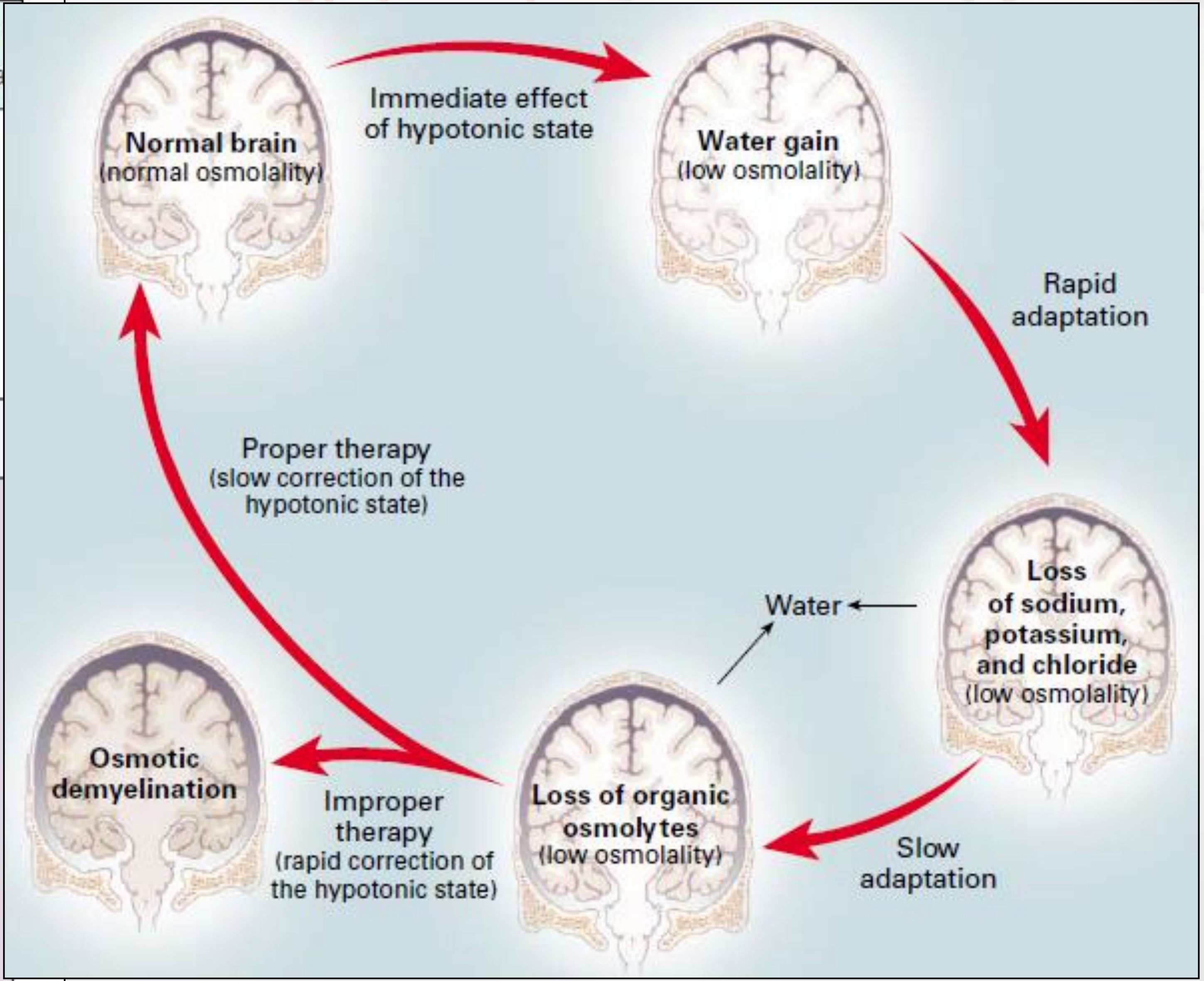


Table 1. Guideline-Recommended Treatment of Severely Symptomatic Hyponatremia With Hypertonic Saline

	US guideline	European guideline
Patients requiring treatment with hypertonic saline	Regardless of duration: • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress) • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progressing to life-threatening complications	Regardless of duration: • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress) • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progressing to life-threatening complications
Rate of increase in serum sodium level desired (goal for change in serum sodium level)	4-6 mEq/L within 1-2 h	5 mEq/L within 1-2 h
Recommended treatment with hypertonic saline (3% sodium chloride)	100-mL bolus via central or peripheral vein over 10 min up to 3 times as needed to attain desired serum sodium level	150-mL bolus via central or peripheral vein over 20 min, repeating this step twice until the desired serum sodium level is achieved
Recommended frequency of measuring serum sodium level	After each bolus and every 4-6 h over the first 24 h	After each bolus and every 6 h over the first 24 h
Recommended increase in serum sodium level that should not be exceeded (correction limit)	At low risk for osmotic demyelination: • 10 mEq/L within first 24 h[a] • 18 mEq/L within first 48 h[a] At high risk for osmotic demyelination: • 8 mEq/L during any 24-h period[b]	At low risk for osmotic demyelination: • 10 mEq/L within first 24 h[a] • 18 mEq/L within first 48 h[a] At high risk for osmotic demyelination: • 8 mEq/L during any 24-h period[b]

JAMA July 19, 2022 Volume 328, Number 3


Rapid onset of acute hypernatremia
Rapid correction of chronic hyponatremia
Rapid increase in plasma sodium concentration
Osmotic demyelination
Extrapontine
Pontine
Demyelination
Neuron


Normal brain (normal osmolality)
Immediate effect of hypotonic state
Water gain (low osmolality)
Rapid adaptation
Loss of sodium, potassium, and chloride (low osmolality)
Water
Slow adaptation
Loss of organic osmolytes (low osmolality)
Improper therapy (rapid correction of the hypotonic state)
Osmotic demyelination
Proper therapy (slow correction of the hypotonic state)

N Engl J Med 2015; 372:55-65

N Engl J Med 2000; 342:1581-1589

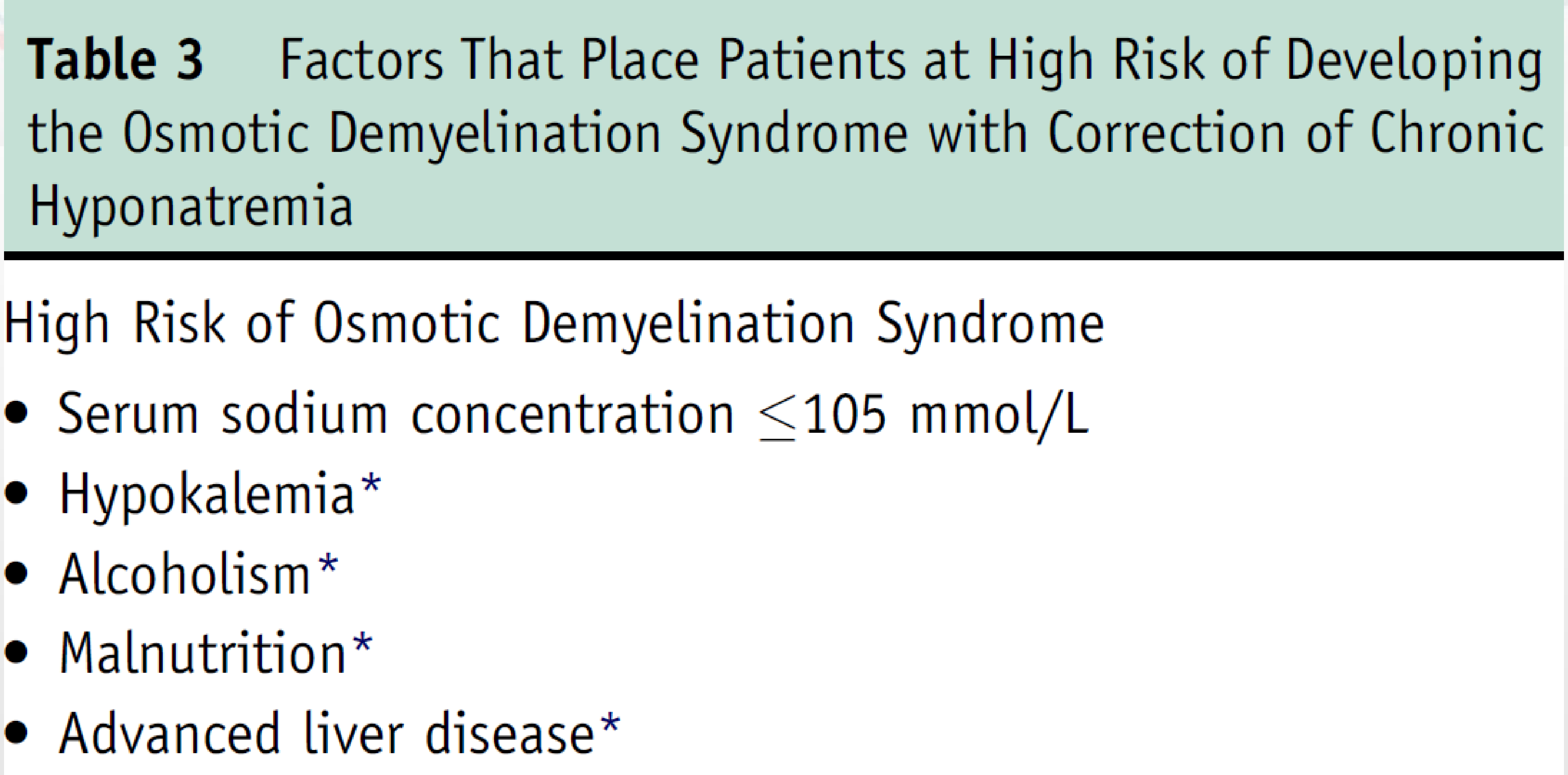


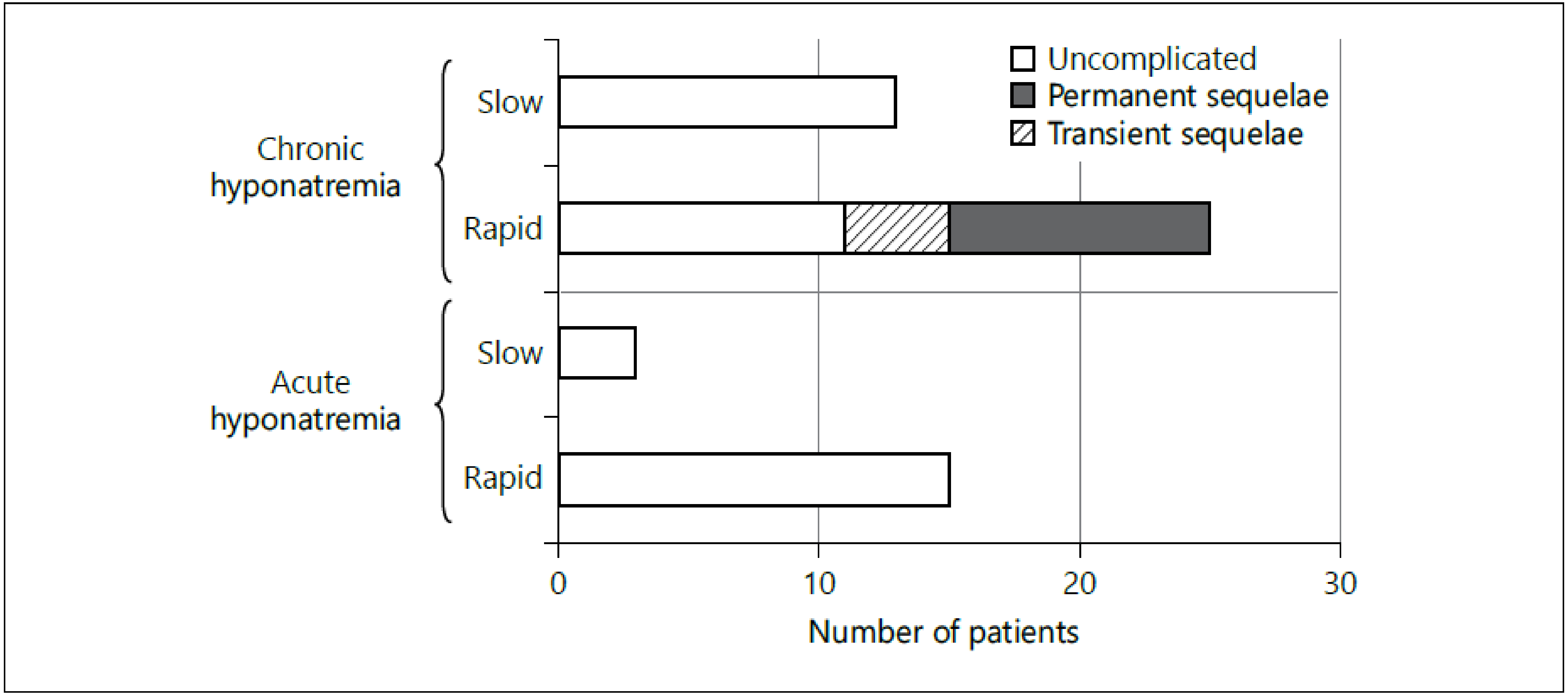
Table 3 Factors That Place Patients at High Risk of Developing the Osmotic Demyelination Syndrome with Correction of Chronic Hyponatremia

High Risk of Osmotic Demyelination Syndrome
• Serum sodium concentration $\leq$105 mmol/L
• Hypokalemia*
• Alcoholism*
• Malnutrition*
• Advanced liver disease*

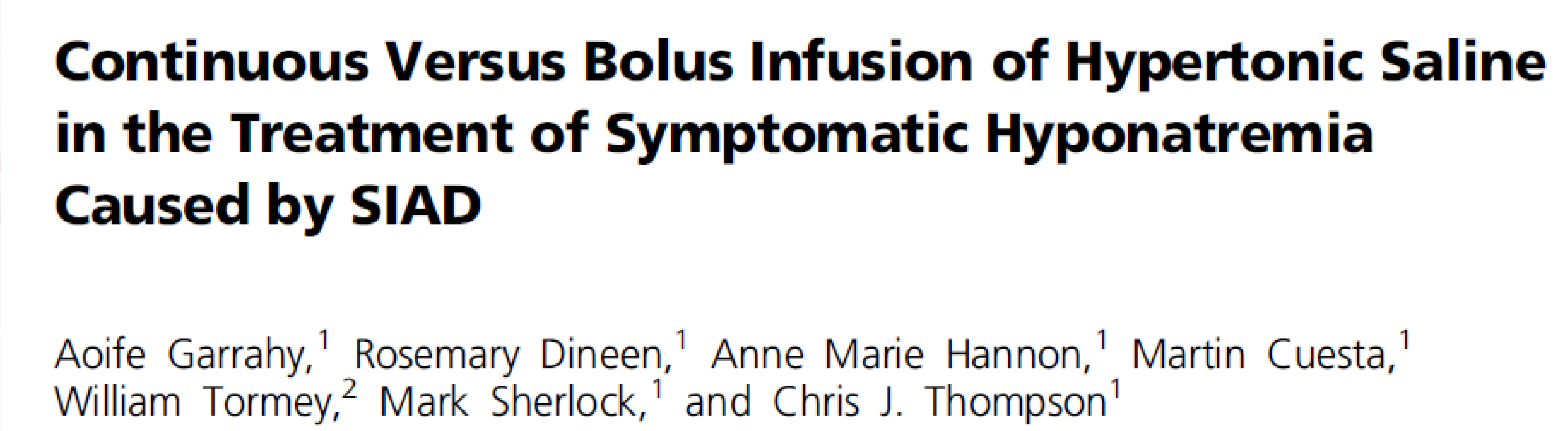
The American Journal of Medicine (2013) 126, S1-S42

Table 1. Single-center series of patients with hyponatremia: more rapid correction is associated with ODS

Author, ref., year	Patients,	Serum	Patients	Correction	Correction rate	Correction
Sterns [37],						
Brunner et a [35], 1990						
Tanneau et [40], 1994						
Ellis [36], 19						
Vu et al. [39]						



Peri A, Thompson CJ Disorders of Fluid and Electrolyte Metabolism. Focus on Hyponatremia. Front Horm Res. 2019, vol 52, pp 130–142



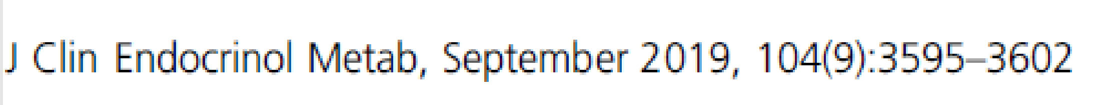
Continuous Versus Bolus Infusion of Hypertonic Saline in the Treatment of Symptomatic Hyponatremia Caused by SIAD

Aoife Garrahy,[1] Rosemary Dineen,[1] Anne Marie Hannon,[1] Martin Cuesta,[1] William Tormey,[2] Mark Sherlock,[1] and Chris J. Thompson[1]

Comparer l'efficacité et l'innocuité de l’administration en bolus par rapport à la perfusion continue du NaCl 3% pour traiter les patients ayant un SIADH avec des symptômes sévères

Na+ < 125 mmol/l

Signes neurologiques : GCS <15, confusion, coma, convulsions



J Clin Endocrinol Metab, September 2019, 104(9):3595–3602

Continuous Versus Bolus Infusion of Hypertonic Saline in the Treatment of Symptomatic Hyponatremia Caused by SIAD

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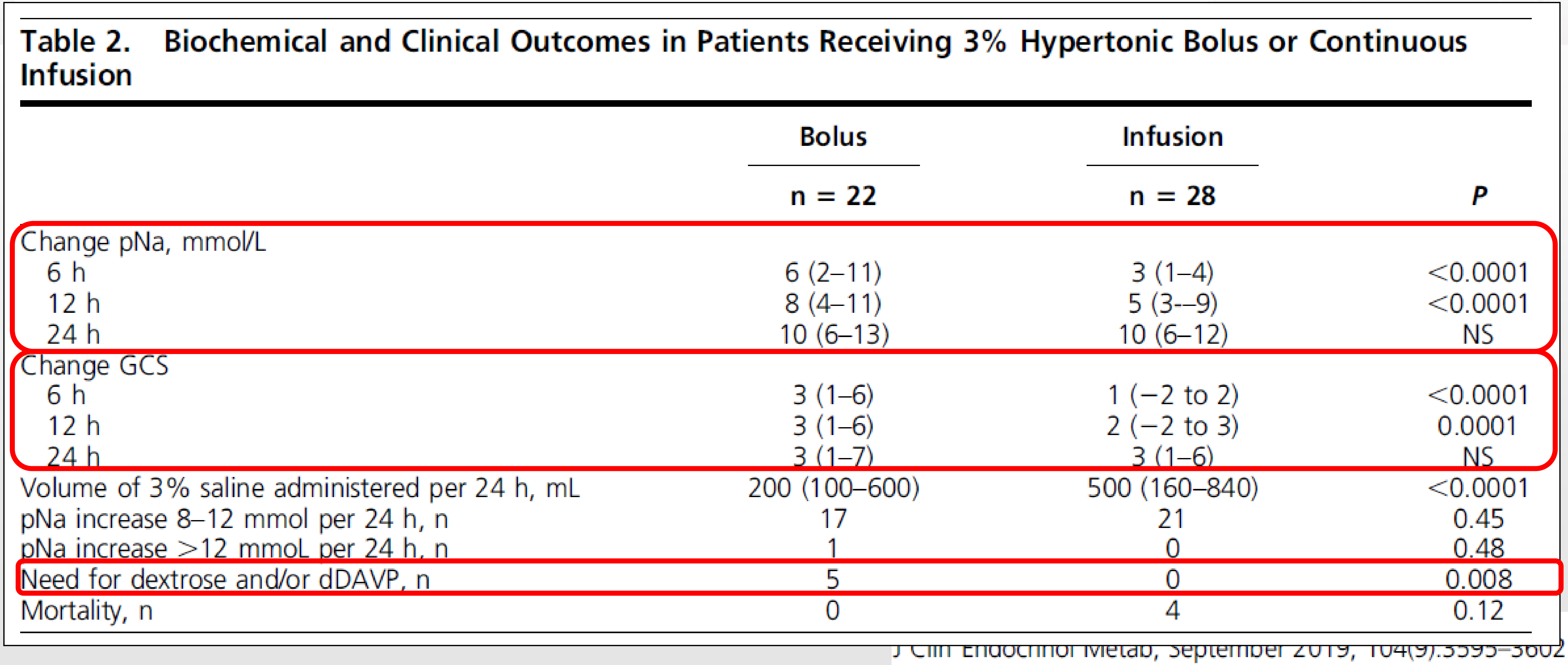


Table 2. Biochemical and Clinical Outcomes in Patients Receiving 3% Hypertonic Bolus or Continuous Infusion

	Bolus n = 22	Infusion n = 28	*P*
Change pNa, mmol/L			
6 h	6 (2–11)	3 (1–4)	<0.0001
12 h	8 (4–11)	5 (3-–9)	<0.0001
24 h	10 (6–13)	10 (6–12)	NS
Change GCS			
6 h	3 (1–6)	1 (−2 to 2)	<0.0001
12 h	3 (1–6)	2 (−2 to 3)	0.0001
24 h	3 (1–7)	3 (1–6)	NS
Volume of 3% saline administered per 24 h, mL	200 (100–600)	500 (160–840)	<0.0001
pNa increase 8–12 mmol per 24 h, n	17	21	0.45
pNa increase >12 mmoL per 24 h, n	1	0	0.48
Need for dextrose and/or dDAVP, n	5	0	0.008
Mortality, n	0	4	0.12

J Clin Endocrinol Metab, September 2019, 104(9):3595–3602

Treatment of symptomatic hyponatremia with hypertonic saline: a real-life observational study

Irina Chifu[1], **Amelie Gerstl**[2], **Björn Lengenfelder**[2,3], **Dominik Schmitt**[2,3], **Nils Nagler**[2,3], **Martin Fassnacht**[1] and **Dirk Weismann**[2]

N = 62 patients (mean sodium level: 118 mEq/L)

Bolus group (n = 36)

150 mL administered once for moderate symptoms or 150 mL administered twice for severe symptoms (per European guideline)

Comparator group (n = 26)

Standard care

Moderate symptoms

17 patients in bolus group vs 16 patients in comparator group (*P* value not provided)

Severe symptoms

19 patients in bolus group vs 10 patients in comparator group (*P* value not provided)

Observed change in serum sodium level

At 24 h: 9 mEq/L in bolus group vs 6 mEq/L in comparator group (difference not statistically significant, *P* value not provided)

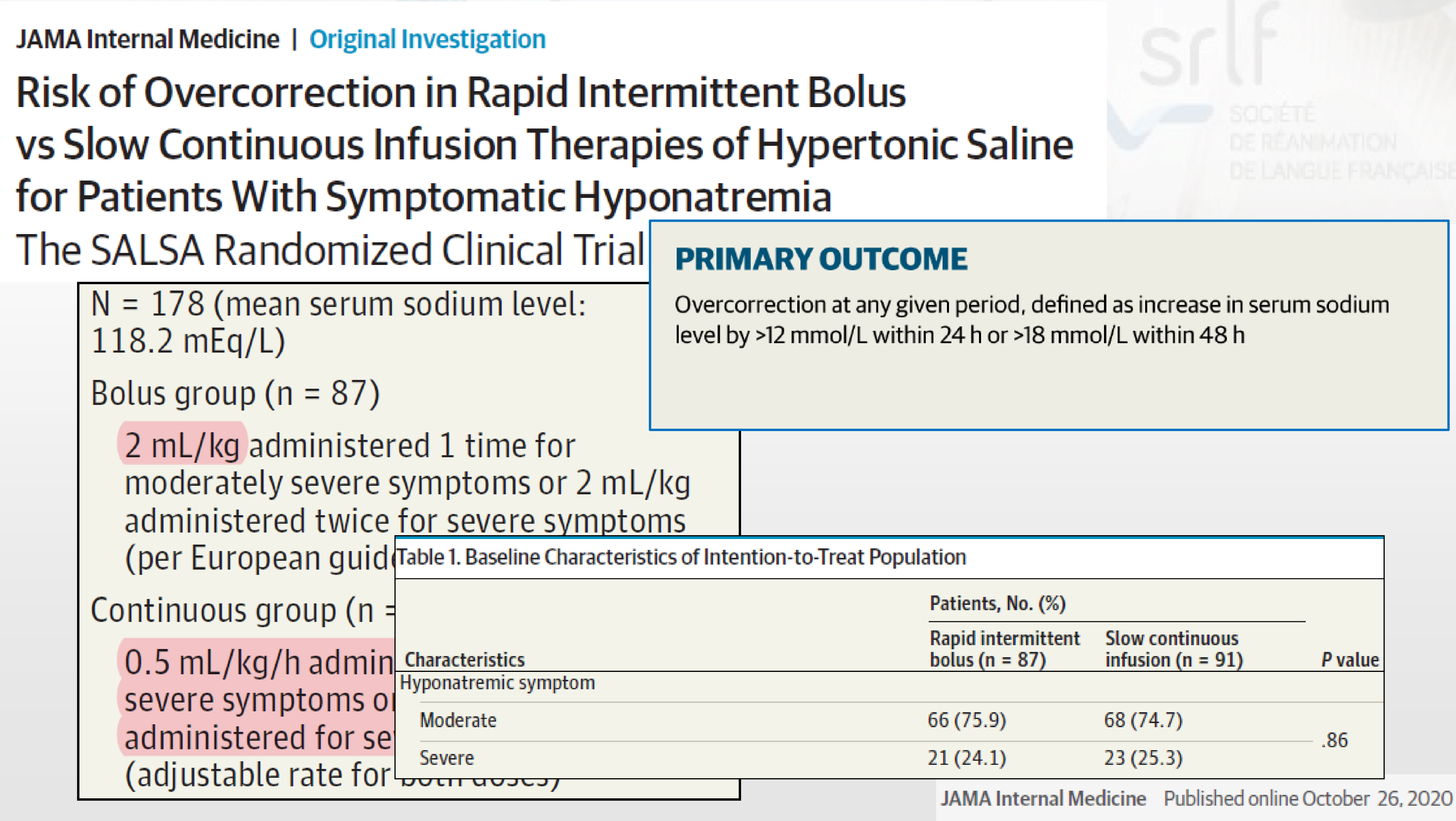
Underwent relowering therapy for serum sodium level

27.8% in bolus group vs 0% in comparator group (*P* value not provided)

Osmotic demyelination

0 cases

European Journal of Endocrinology (2021) **184**, 647–655



JAMA Internal Medicine | Original Investigation

Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia

The SALSA Randomized Clinical Trial

N = 178 (mean serum sodium level: 118.2 mEq/L)

Bolus group (n = 87)

2 mL/kg administered 1 time for moderately severe symptoms or 2 mL/kg administered twice for severe symptoms (per European guid

Continuous group (n =

0.5 mL/kg/h admin
severe symptoms o
administered for se
(adjustable rate for

PRIMARY OUTCOME

Overcorrection at any given period, defined as increase in serum sodium level by >12 mmol/L within 24 h or >18 mmol/L within 48 h

Table 1. Baseline Characteristics of Intention-to-Treat Population

	Patients, No. (%)		
Characteristics	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)	*P* value
Hyponatremic symptom			
Moderate	66 (75.9)	68 (74.7)	.86
Severe	21 (24.1)	23 (25.3)	

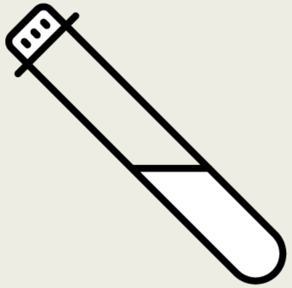
JAMA Internal Medicine Published online October 26, 2020

JAMA Internal Medicine

RCT: Risk of Overcorrection in Rapid Intermittent Bolus v Symptomatic Hyponatremia

POPULATION

80 Men, 98 Women

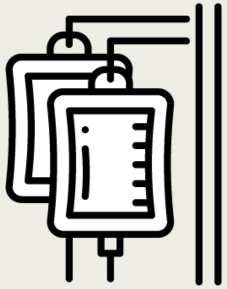


Adults aged >18 y with symptoms of hyponatremia and glucose-corrected serum sodium ≤125 mmol/L

Mean (SD) age: 73.1 (12.2) y

INTERVENTION

178 Patients randomized



87 Rapid intermittent bolus
Hypertonic saline, 3%, infusion of 2 mL/kg over 20 min every 6 h

91 Slow conti
Hypertonic sa
continuous inf
0.5-1 mL/kg/h

SETTINGS / LOCATIONS

3 General hospitals in the Republic of Korea

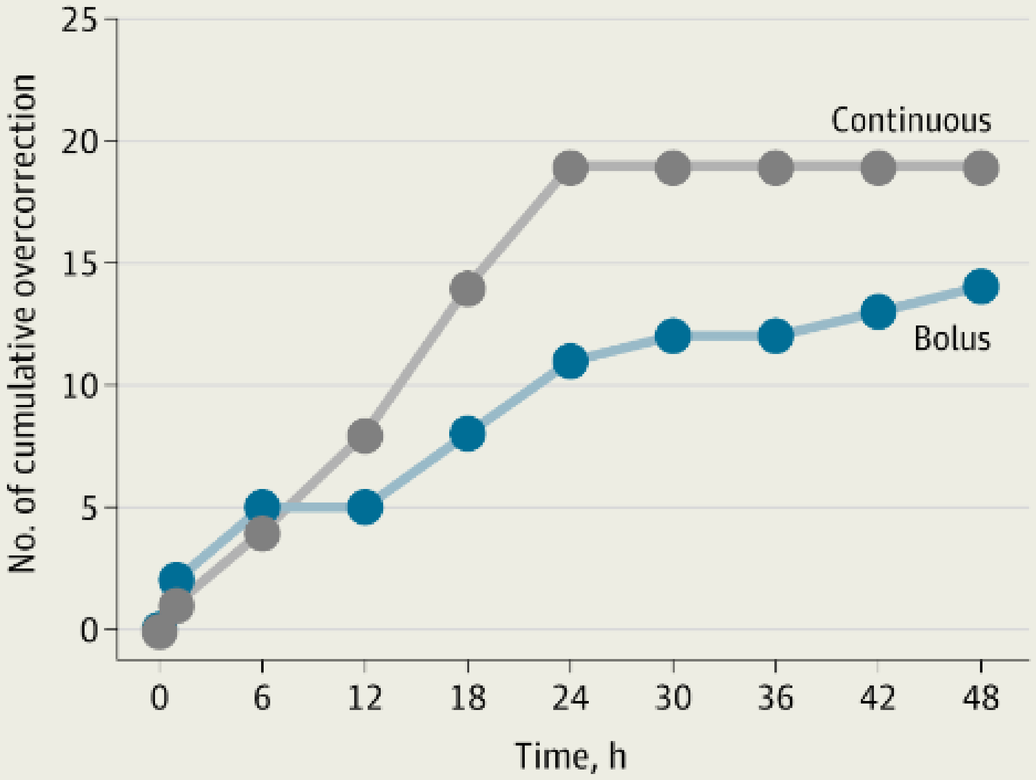
PRIMARY OUTCOME

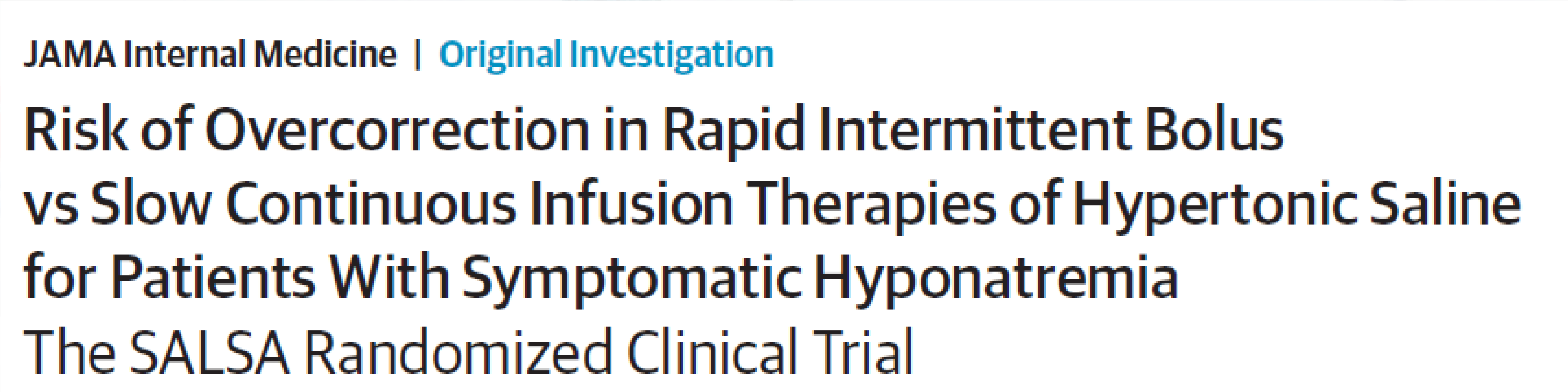
Overcorrection at any given period, defined as increase i level by >12 mmol/L within 24 h or >18 mmol/L within 48

Baek SH, Jo YH, Ahn S, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion th
SALSA randomized clinical trial. *JAMA Intern Med.* Published online October 26, 2020. doi:10.1001/jamainte

FINDINGS

Both rapid intermittent bolus and slow continuous infusion for treating symptomatic hyponatremia are effective and safe with no difference in overcorrection risk (17.2% vs 24.2%, respectively; absolute risk difference, −6.9% (95% CI, −18.8% to 4.9%); $P = .26$)




JAMA Internal Medicine | Original Investigation

Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia

The SALSA Randomized Clinical Trial

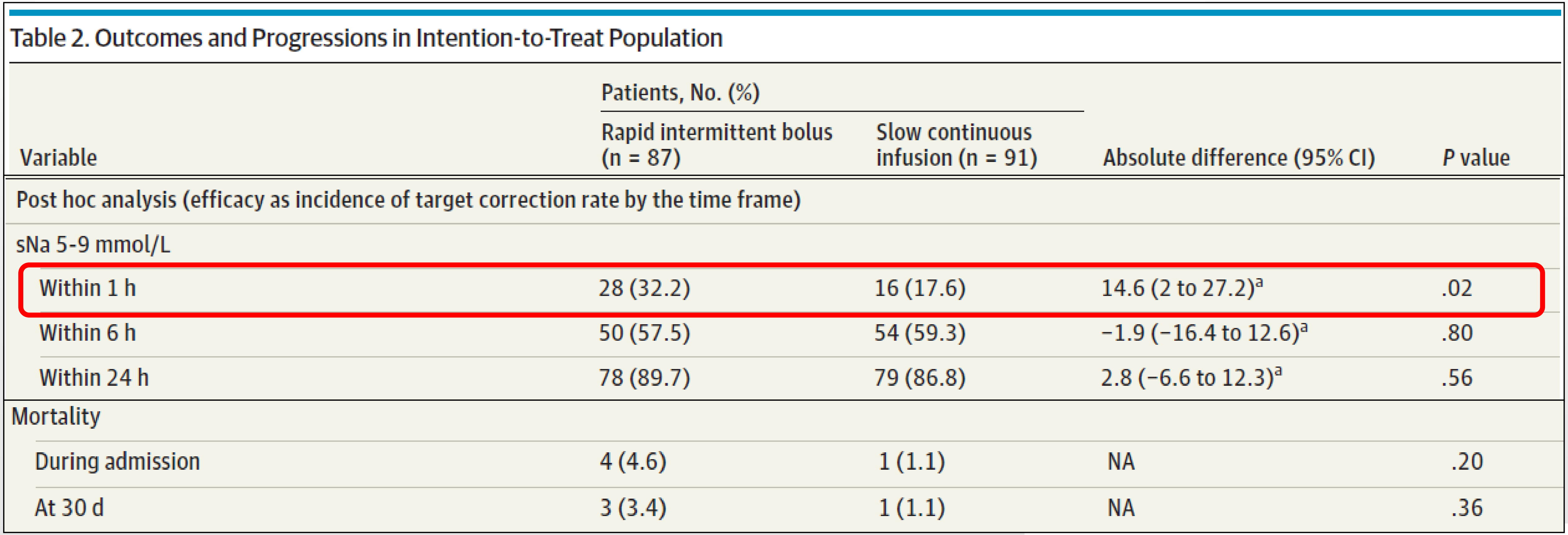
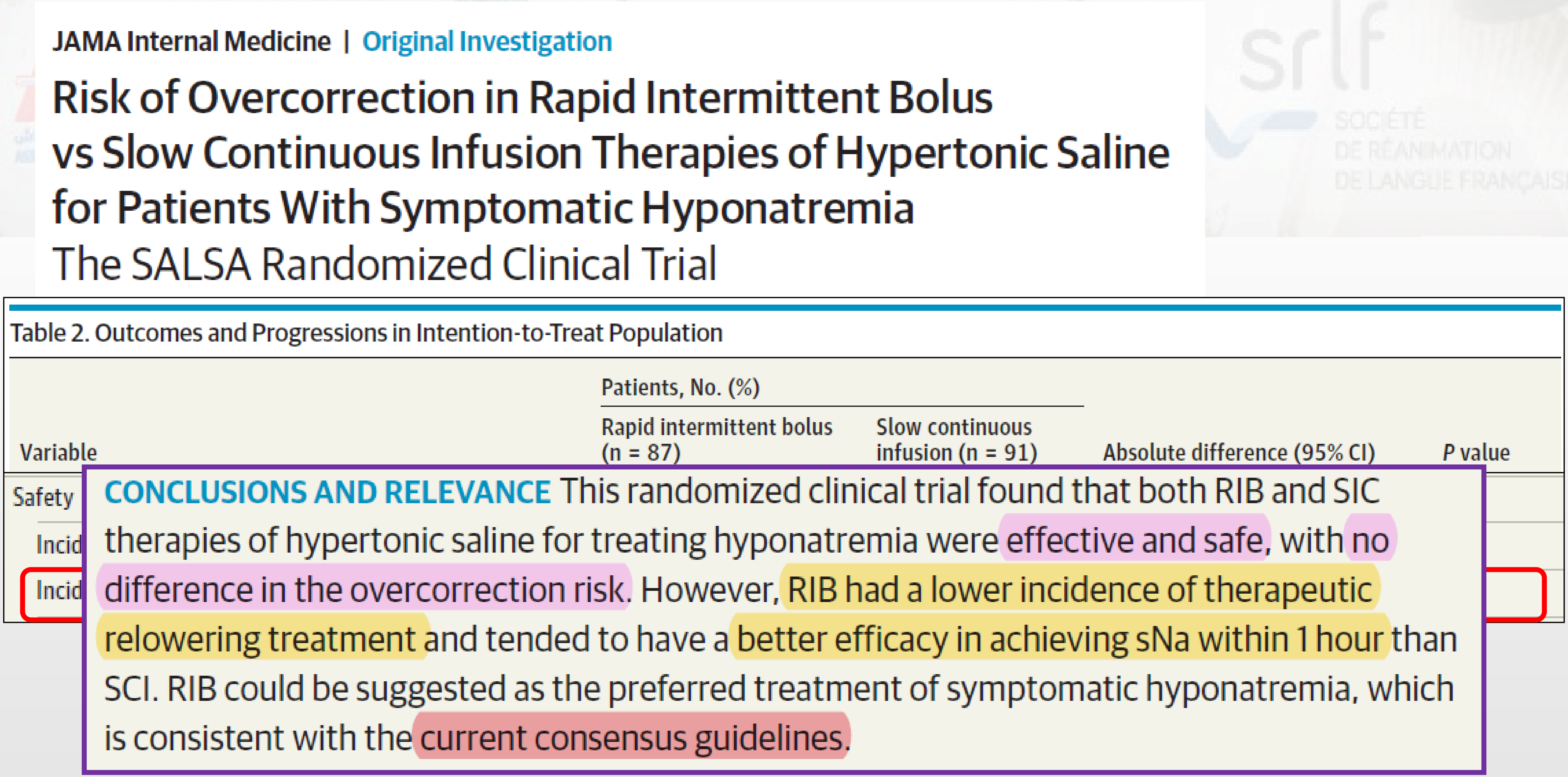


Table 2. Outcomes and Progressions in Intention-to-Treat Population

Variable	Patients, No. (%)		Absolute difference (95% CI)	P value
	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)		
Post hoc analysis (efficacy as incidence of target correction rate by the time frame)				
sNa 5-9 mmol/L				
Within 1 h	28 (32.2)	16 (17.6)	14.6 (2 to 27.2)[a]	.02
Within 6 h	50 (57.5)	54 (59.3)	−1.9 (−16.4 to 12.6)[a]	.80
Within 24 h	78 (89.7)	79 (86.8)	2.8 (−6.6 to 12.3)[a]	.56
Mortality				
During admission	4 (4.6)	1 (1.1)	NA	.20
At 30 d	3 (3.4)	1 (1.1)	NA	.36

JAMA Internal Medicine Published online October 26, 2020



JAMA Internal Medicine | Original Investigation

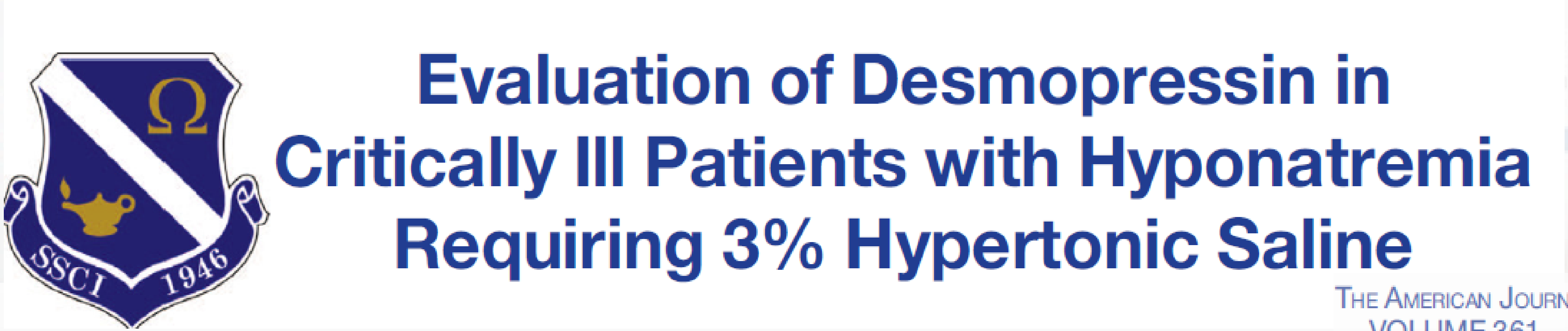
Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia
The SALSA Randomized Clinical Trial

Table 2. Outcomes and Progressions in Intention-to-Treat Population

	Patients, No. (%)			
Variable	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)	Absolute difference (95% CI)	*P* value
Safety				
Incid				
Incid				

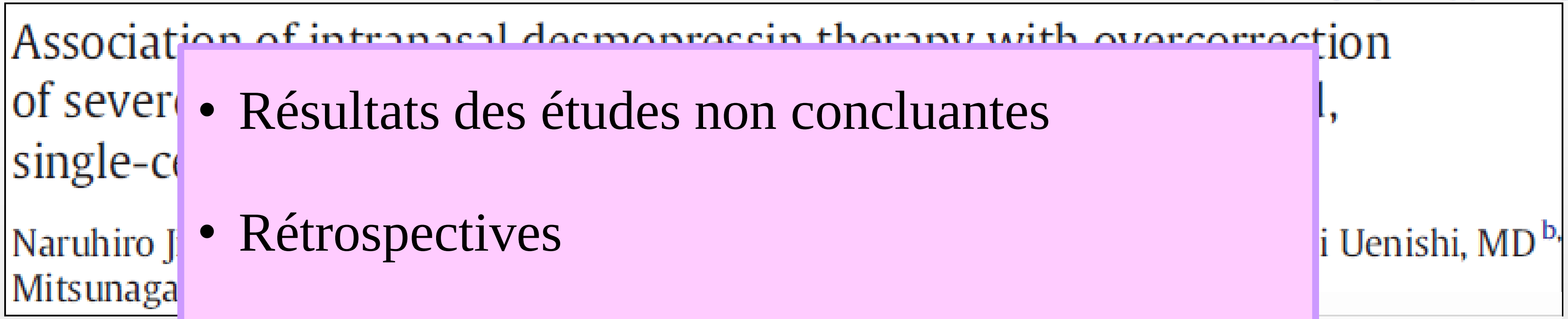
CONCLUSIONS AND RELEVANCE This randomized clinical trial found that both RIB and SIC therapies of hypertonic saline for treating hyponatremia were effective and safe, with no difference in the overcorrection risk. However, RIB had a lower incidence of therapeutic relowering treatment and tended to have a better efficacy in achieving sNa within 1 hour than SCI. RIB could be suggested as the preferred treatment of symptomatic hyponatremia, which is consistent with the current consensus guidelines.

JAMA Internal Medicine Published online October 26, 2020



Evaluation of Desmopressin in Critically Ill Patients with Hyponatremia Requiring 3% Hypertonic Saline

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES
VOLUME 361 NUMBER 6 JUNE 2021



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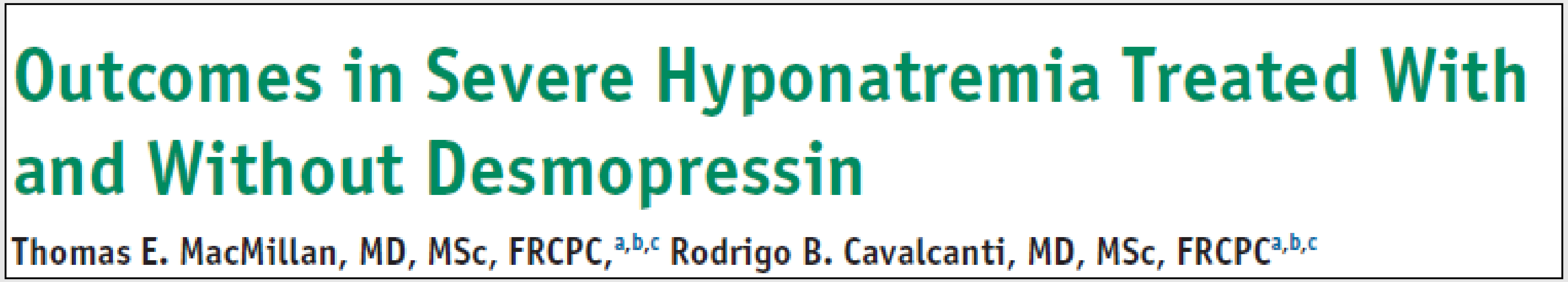
Naruhiro J... ...i Uenishi, MD[b]...
Mitsunaga...

(2021) 53–61

- Résultats des études non concluantes
- Rétrospectives
- Nécessités d’études randomisées

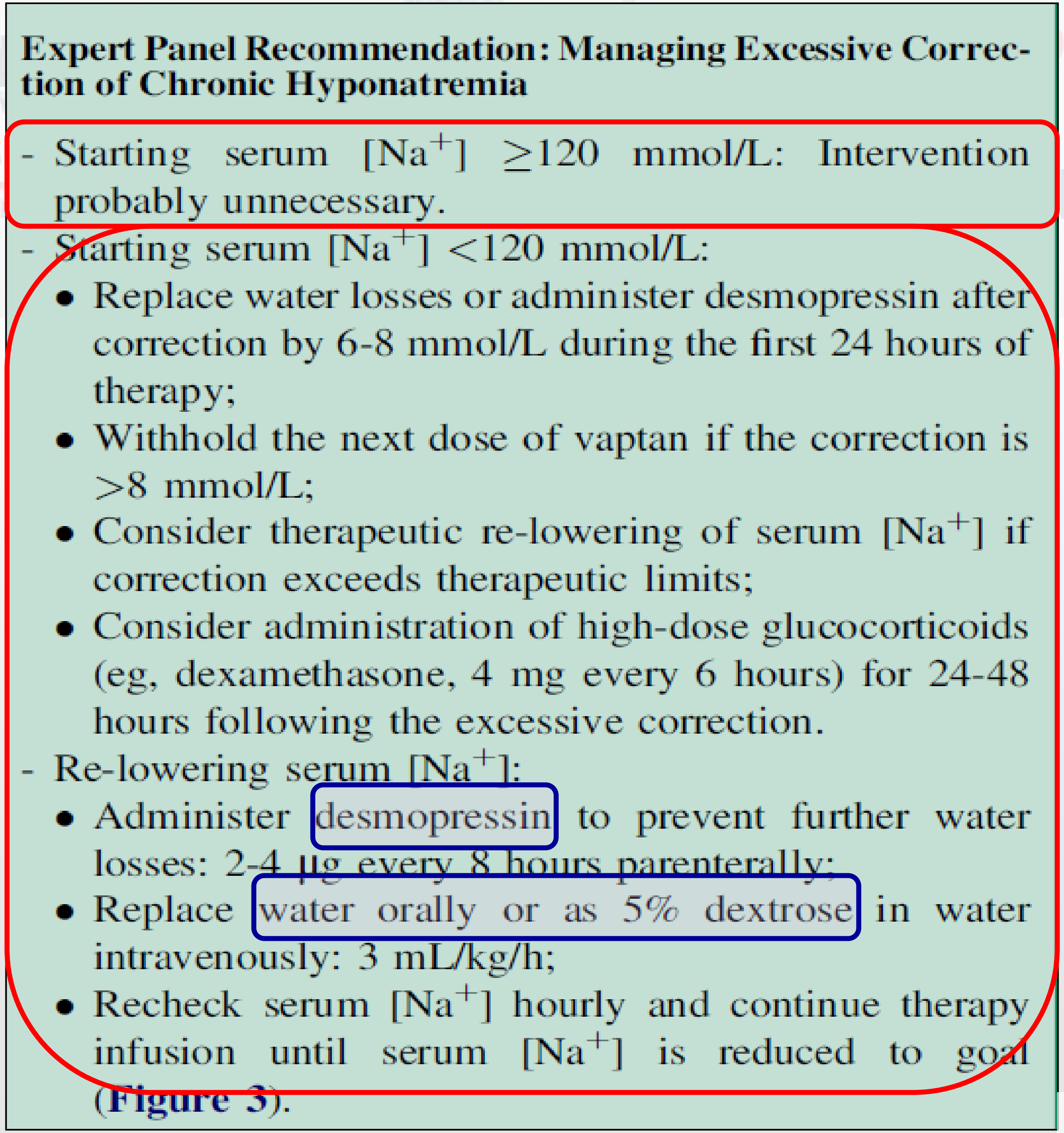


Outcomes in Severe Hyponatremia Treated With and Without Desmopressin

Thomas E. MacMillan, MD, MSc, FRCPC,[a,b,c] Rodrigo B. Cavalcanti, MD, MSc, FRCPC[a,b,c]

THE AMERICAN JOURNAL of MEDICINE®

The American Journal of Medicine (2018) 131, 317.e1–317.e10



Expert Panel Recommendation: Managing Excessive Correction of Chronic Hyponatremia

- Starting serum [Na^+] ≥120 mmol/L: Intervention probably unnecessary.
- Starting serum [Na^+] <120 mmol/L:
  - Replace water losses or administer desmopressin after correction by 6-8 mmol/L during the first 24 hours of therapy;
  - Withhold the next dose of vaptan if the correction is >8 mmol/L;
  - Consider therapeutic re-lowering of serum [Na^+] if correction exceeds therapeutic limits;
  - Consider administration of high-dose glucocorticoids (eg, dexamethasone, 4 mg every 6 hours) for 24-48 hours following the excessive correction.
- Re-lowering serum [Na^+]:
  - Administer desmopressin to prevent further water losses: 2-4 µg every 8 hours parenterally;
  - Replace water orally or as 5% dextrose in water intravenously: 3 mL/kg/h;
  - Recheck serum [Na^+] hourly and continue therapy infusion until serum [Na^+] is reduced to goal (**Figure 3**).

The American Journal of Medicine (2013) 126, S1-S42

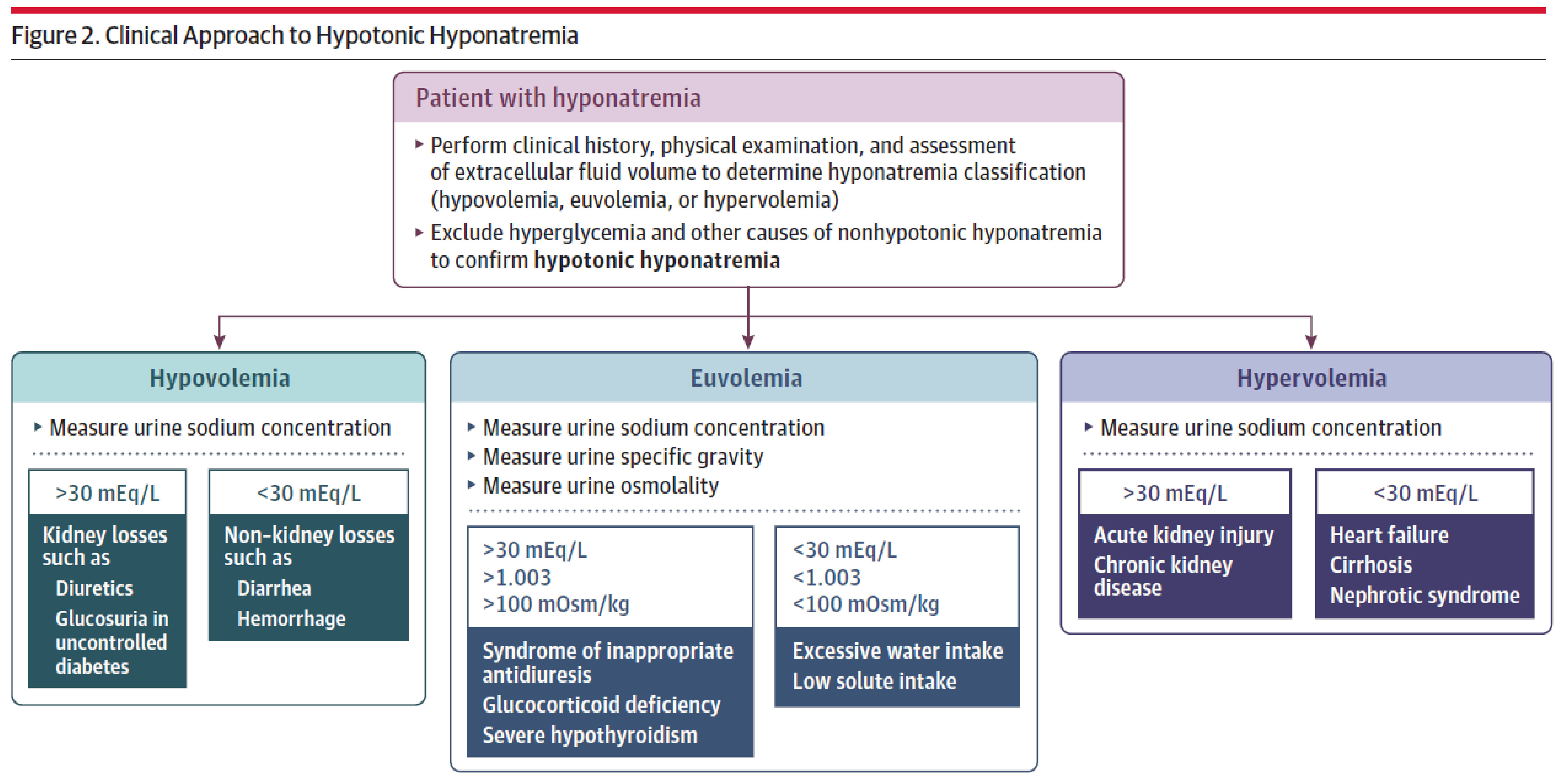


Figure 2. Clinical Approach to Hypotonic Hyponatremia

Patient with hyponatremia

- Perform clinical history, physical examination, and assessment of extracellular fluid volume to determine hyponatremia classification (hypovolemia, euvolemia, or hypervolemia)
- Exclude hyperglycemia and other causes of nonhypotonic hyponatremia to confirm **hypotonic hyponatremia**

Hypovolemia

- Measure urine sodium concentration

>30 mEq/L

Kidney losses such as
- Diuretics
- Glucosuria in uncontrolled diabetes

<30 mEq/L

Non-kidney losses such as
- Diarrhea
- Hemorrhage

Euvolemia

- Measure urine sodium concentration
- Measure urine specific gravity
- Measure urine osmolality

>30 mEq/L
>1.003
>100 mOsm/kg

Syndrome of inappropriate antidiuresis
Glucocorticoid deficiency
Severe hypothyroidism

<30 mEq/L
<1.003
<100 mOsm/kg

Excessive water intake
Low solute intake

Hypervolemia

- Measure urine sodium concentration

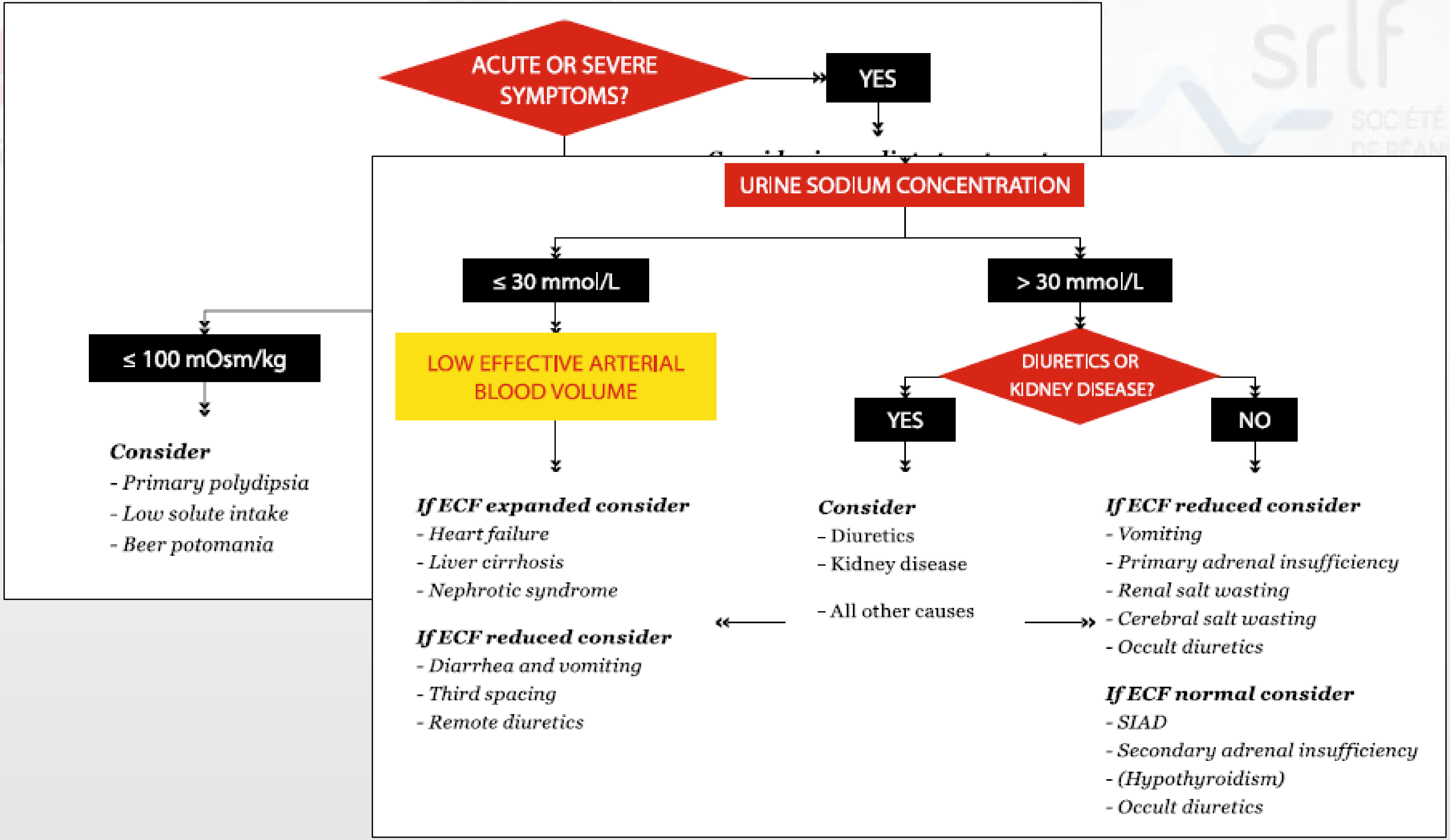
>30 mEq/L

Acute kidney injury
Chronic kidney disease

<30 mEq/L

Heart failure
Cirrhosis
Nephrotic syndrome

Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10)(suppl 1):S1-S42



ACUTE OR SEVERE SYMPTOMS?

YES

≤ 100 mOsm/kg

Consider
- *Primary polydipsia*
- *Low solute intake*
- *Beer potomania*

URINE SODIUM CONCENTRATION

≤ 30 mmol/L

LOW EFFECTIVE ARTERIAL BLOOD VOLUME

If ECF expanded consider
- *Heart failure*
- *Liver cirrhosis*
- *Nephrotic syndrome*

If ECF reduced consider
- *Diarrhea and vomiting*
- *Third spacing*
- *Remote diuretics*

> 30 mmol/L

DIURETICS OR KIDNEY DISEASE?

YES

Consider
- Diuretics
- Kidney disease

- All other causes

NO

If ECF reduced consider
- *Vomiting*
- *Primary adrenal insufficiency*
- *Renal salt wasting*
- *Cerebral salt wasting*
- *Occult diuretics*

If ECF normal consider
- *SIAD*
- *Secondary adrenal insufficiency*
- *(Hypothyroidism)*
- *Occult diuretics*

Intensive Care Med (2014) 40:320–331

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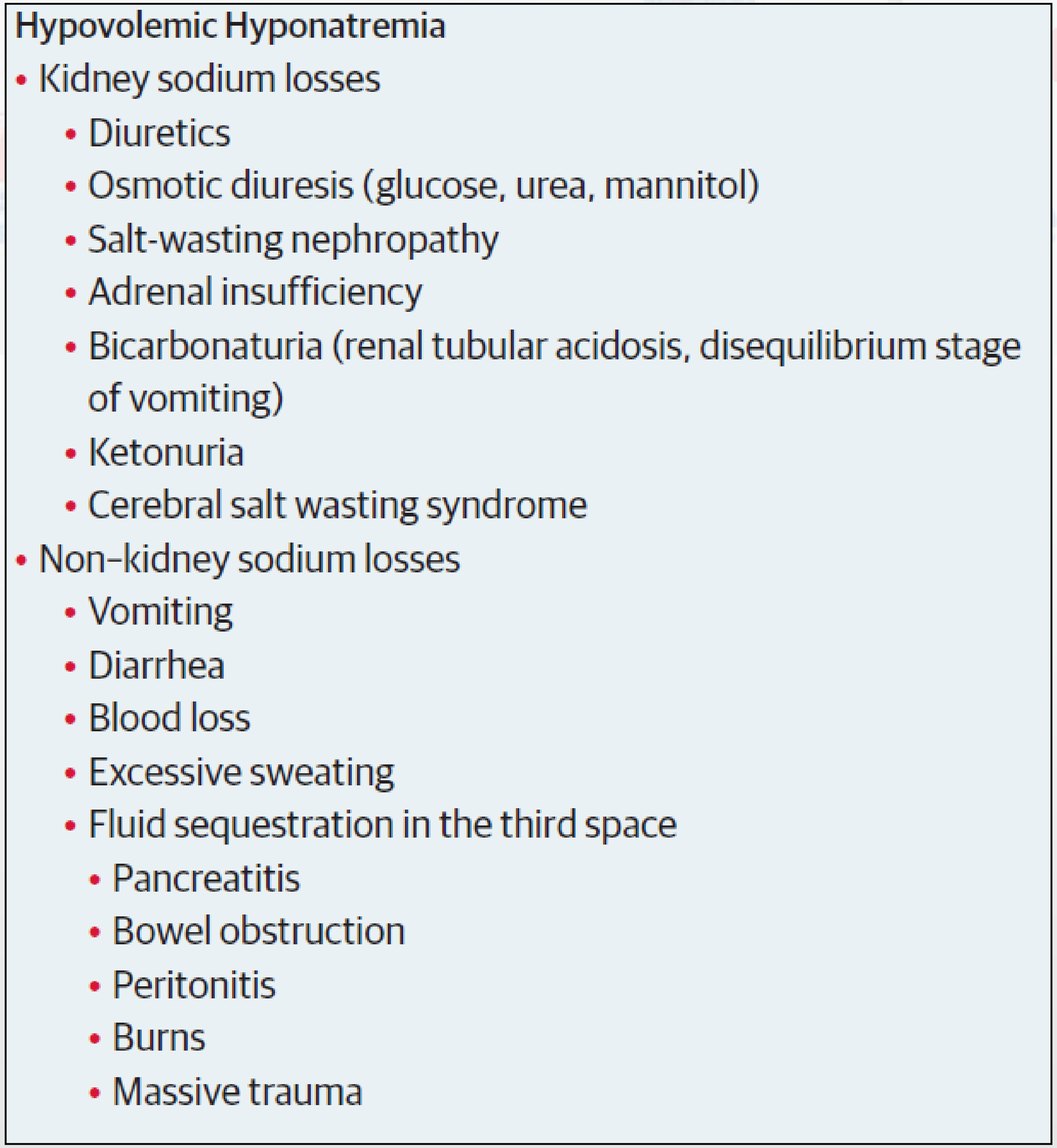
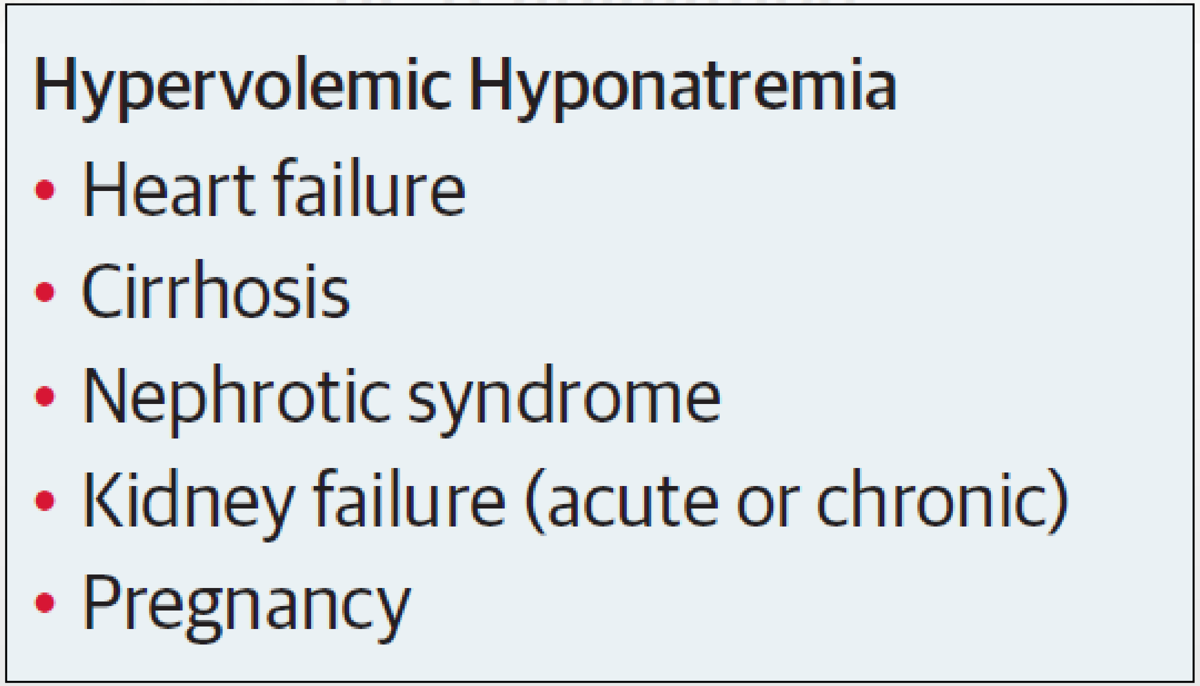


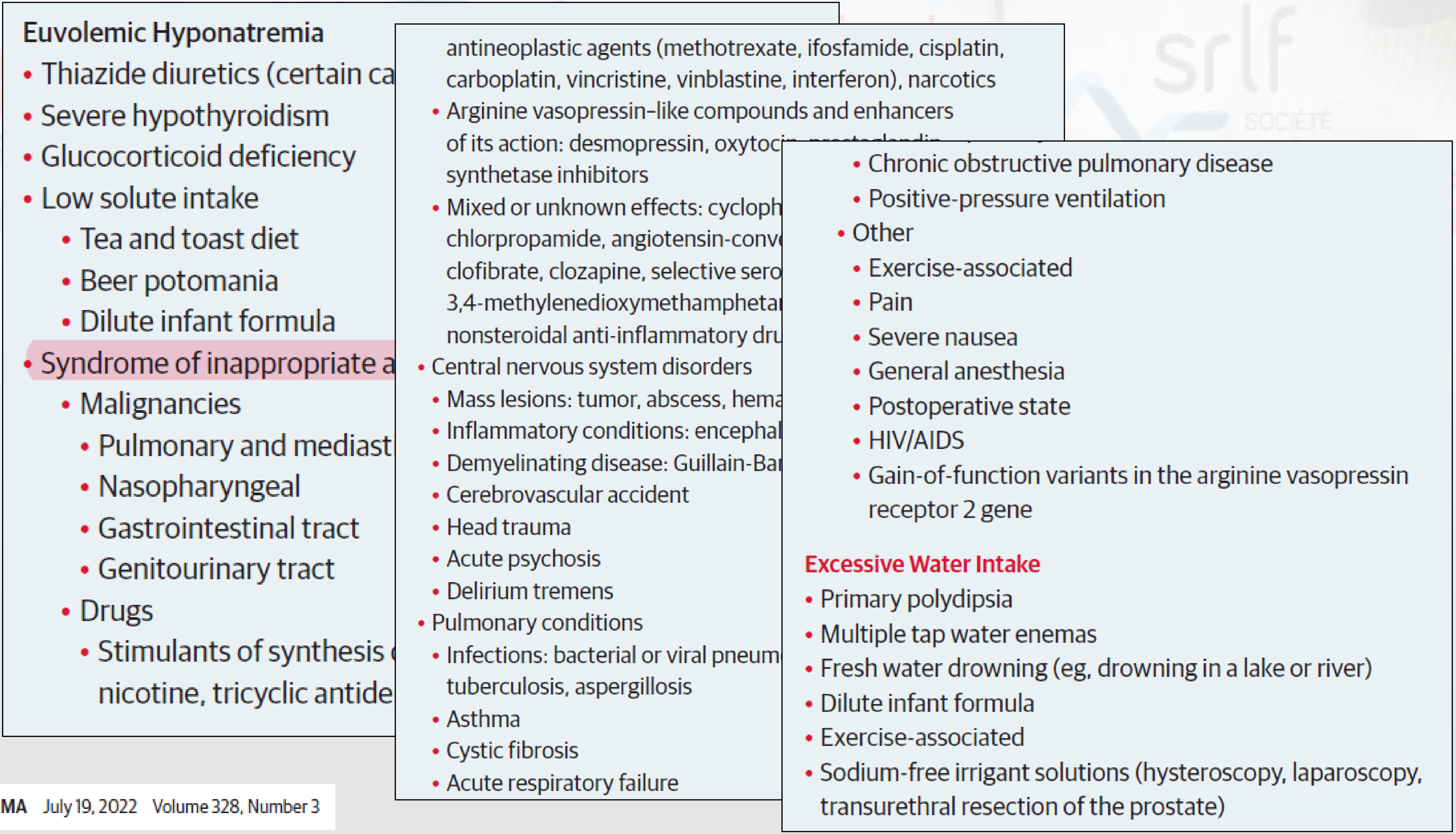
Hypovolemic Hyponatremia

- Kidney sodium losses
  - Diuretics
  - Osmotic diuresis (glucose, urea, mannitol)
  - Salt-wasting nephropathy
  - Adrenal insufficiency
  - Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)
  - Ketonuria
  - Cerebral salt wasting syndrome
- Non-kidney sodium losses
  - Vomiting
  - Diarrhea
  - Blood loss
  - Excessive sweating
  - Fluid sequestration in the third space
    - Pancreatitis
    - Bowel obstruction
    - Peritonitis
    - Burns
    - Massive trauma



Hypervolemic Hyponatremia

- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Kidney failure (acute or chronic)
- Pregnancy



Euvolemic Hyponatremia

- Thiazide diuretics (certain ca
- Severe hypothyroidism
- Glucocorticoid deficiency
- Low solute intake
  - Tea and toast diet
  - Beer potomania
  - Dilute infant formula
- Syndrome of inappropriate a
  - Malignancies
    - Pulmonary and mediast
    - Nasopharyngeal
    - Gastrointestinal tract
    - Genitourinary tract
  - Drugs
    - Stimulants of synthesis
      nicotine, tricyclic antide

antineoplastic agents (methotrexate, ifosfamide, cisplatin, carboplatin, vincristine, vinblastine, interferon), narcotics

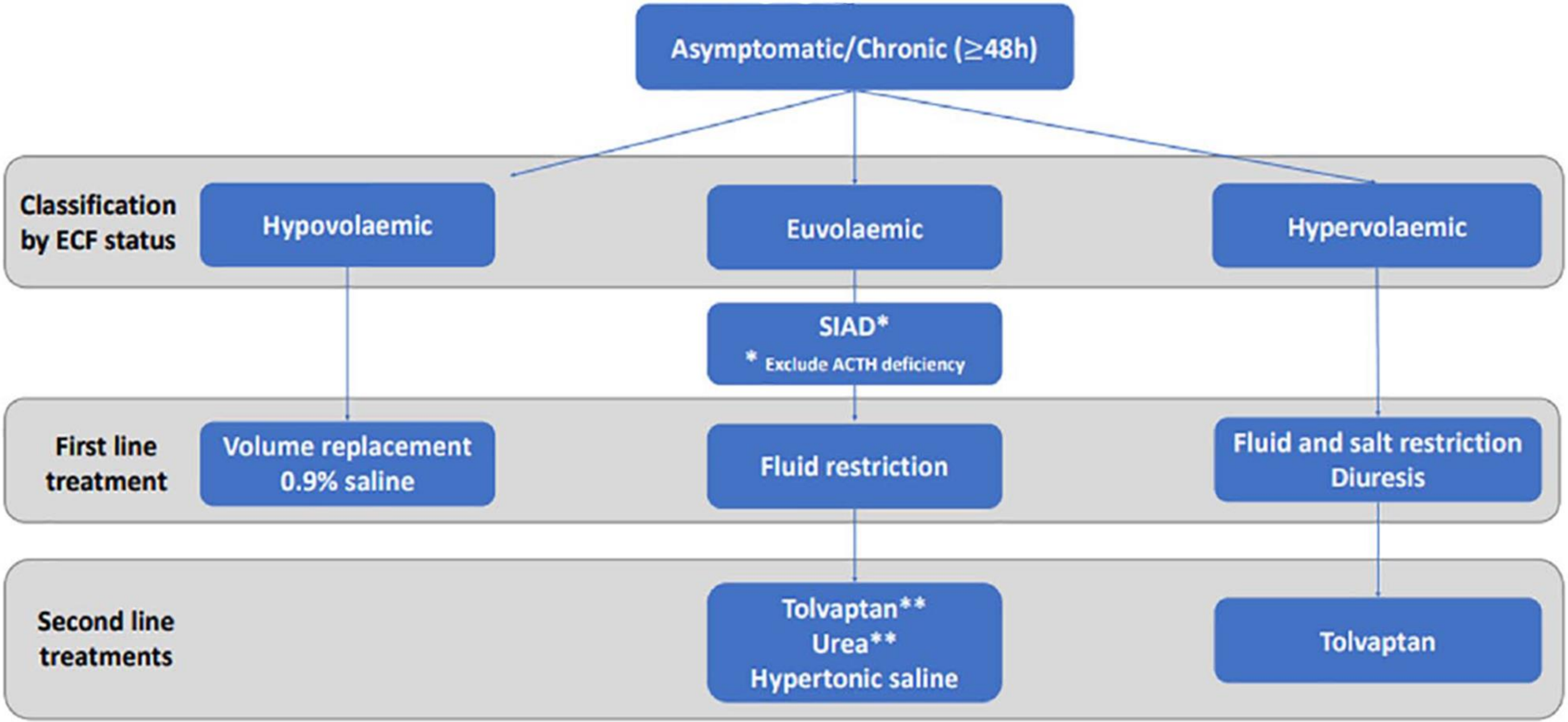
- Arginine vasopressin–like compounds and enhancers of its action: desmopressin, oxytoc
  synthetase inhibitors
- Mixed or unknown effects: cycloph
  chlorpropamide, angiotensin-conve
  clofibrate, clozapine, selective sero
  3,4-methylenedioxymethamphetar
  nonsteroidal anti-inflammatory dru
- Central nervous system disorders
  - Mass lesions: tumor, abscess, hema
  - Inflammatory conditions: encephal
  - Demyelinating disease: Guillain-Bar
  - Cerebrovascular accident
  - Head trauma
  - Acute psychosis
  - Delirium tremens
- Pulmonary conditions
  - Infections: bacterial or viral pneum
    tuberculosis, aspergillosis
  - Asthma
  - Cystic fibrosis
  - Acute respiratory failure

  - Chronic obstructive pulmonary disease
  - Positive-pressure ventilation
- Other
  - Exercise-associated
  - Pain
  - Severe nausea
  - General anesthesia
  - Postoperative state
  - HIV/AIDS
  - Gain-of-function variants in the arginine vasopressin receptor 2 gene

Excessive Water Intake

- Primary polydipsia
- Multiple tap water enemas
- Fresh water drowning (eg, drowning in a lake or river)
- Dilute infant formula
- Exercise-associated
- Sodium-free irrigant solutions (hysteroscopy, laparoscopy, transurethral resection of the prostate)

JAMA July 19, 2022 Volume 328, Number 3



Asymptomatic/Chronic (≥48h)

Classification by ECF status
- Hypovolaemic
- Euvolaemic
  - SIAD*
  - * Exclude ACTH deficiency
- Hypervolaemic

First line treatment
- Hypovolaemic: Volume replacement 0.9% saline
- Euvolaemic: Fluid restriction
- Hypervolaemic: Fluid and salt restriction Diuresis

Second line treatments
- Euvolaemic: Tolvaptan** Urea** Hypertonic saline
- Hypervolaemic: Tolvaptan

Ther Adv Endocrinol Metab 2022, Vol. 13: 1–16

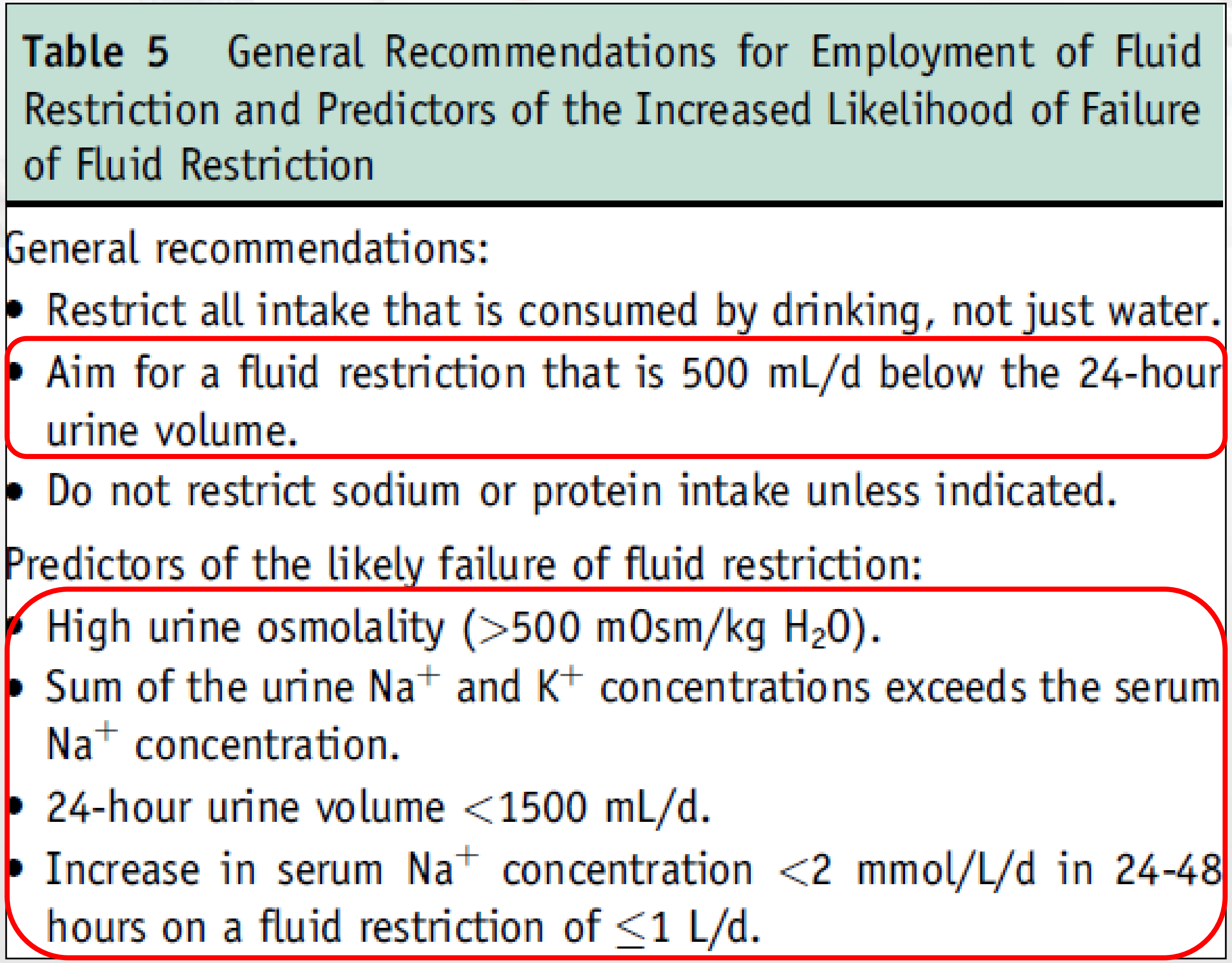


Table 5 General Recommendations for Employment of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction

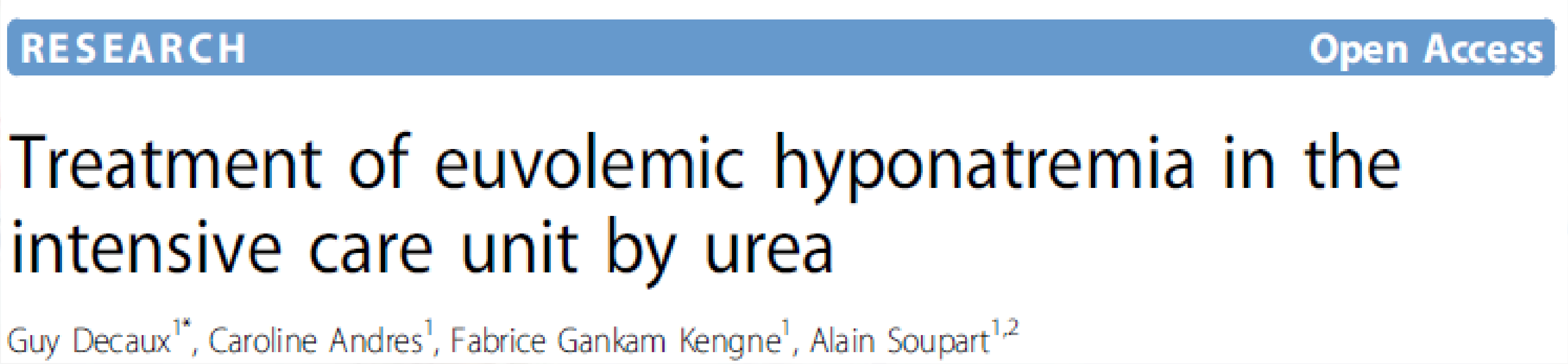
General recommendations:

- Restrict all intake that is consumed by drinking, not just water.
- Aim for a fluid restriction that is 500 mL/d below the 24-hour urine volume.
- Do not restrict sodium or protein intake unless indicated.

Predictors of the likely failure of fluid restriction:

- High urine osmolality (>500 mOsm/kg H_2O).
- Sum of the urine Na^+ and K^+ concentrations exceeds the serum Na^+ concentration.
- 24-hour urine volume <1500 mL/d.
- Increase in serum Na^+ concentration <2 mmol/L/d in 24-48 hours on a fluid restriction of ≤1 L/d.

The American Journal of Medicine (2013) 126, S1-S42



RESEARCH Open Access

Treatment of euvolemic hyponatremia in the intensive care unit by urea

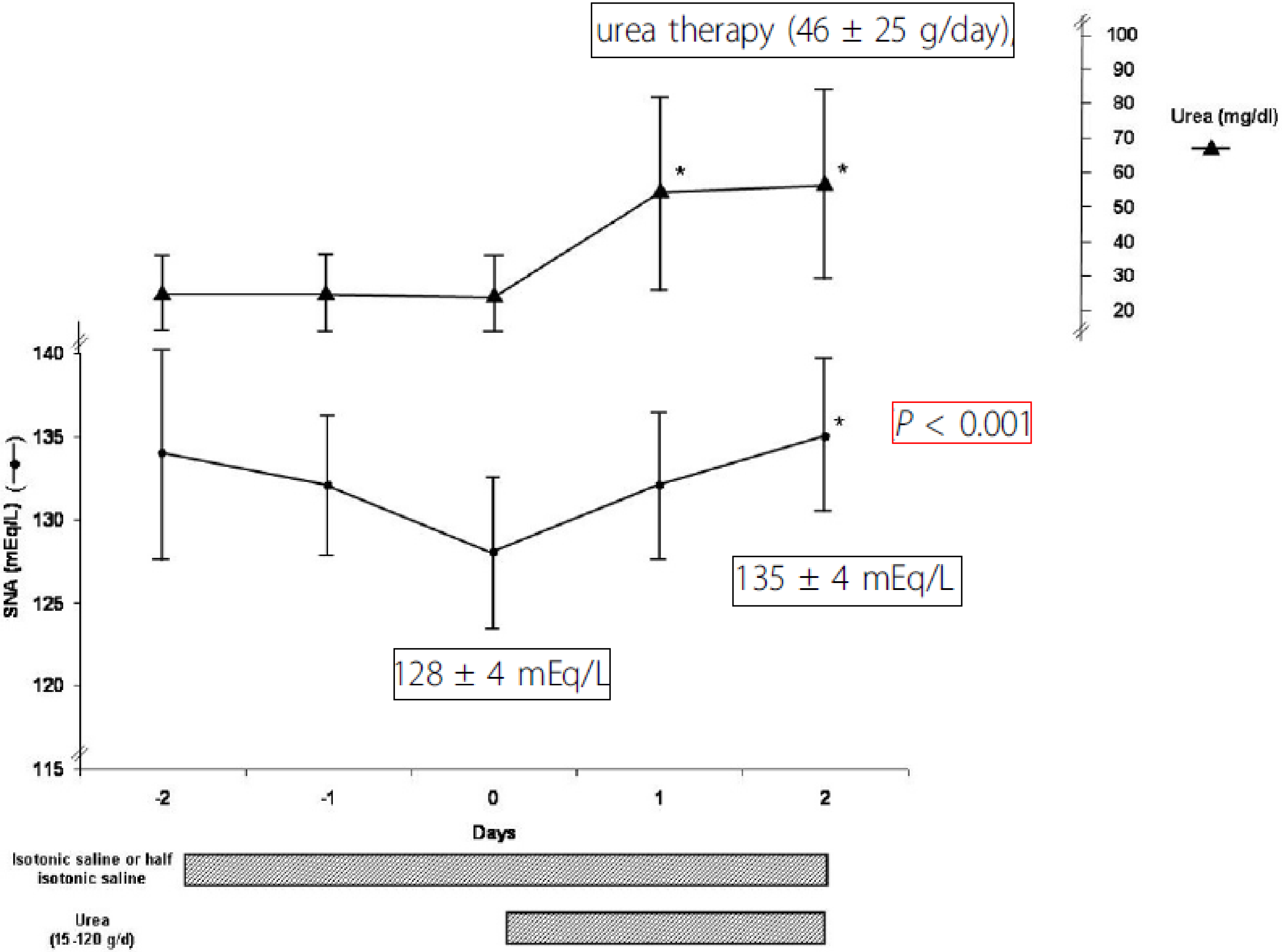
Guy Decaux[1*], Caroline Andres[1], Fabrice Gankam Kengne[1], Alain Soupart[1,2]

CRITICAL CARE

- 50 patients groupe hyponatrémie modérée
- Na+ = 128 ± 4 mEq/L
- SIADH

- 35 patients groupe hyponatrémie sévère
- Na+ = 111 ± 3 mEq/L

Decaux et al. Critical Care 2010, 14:R184



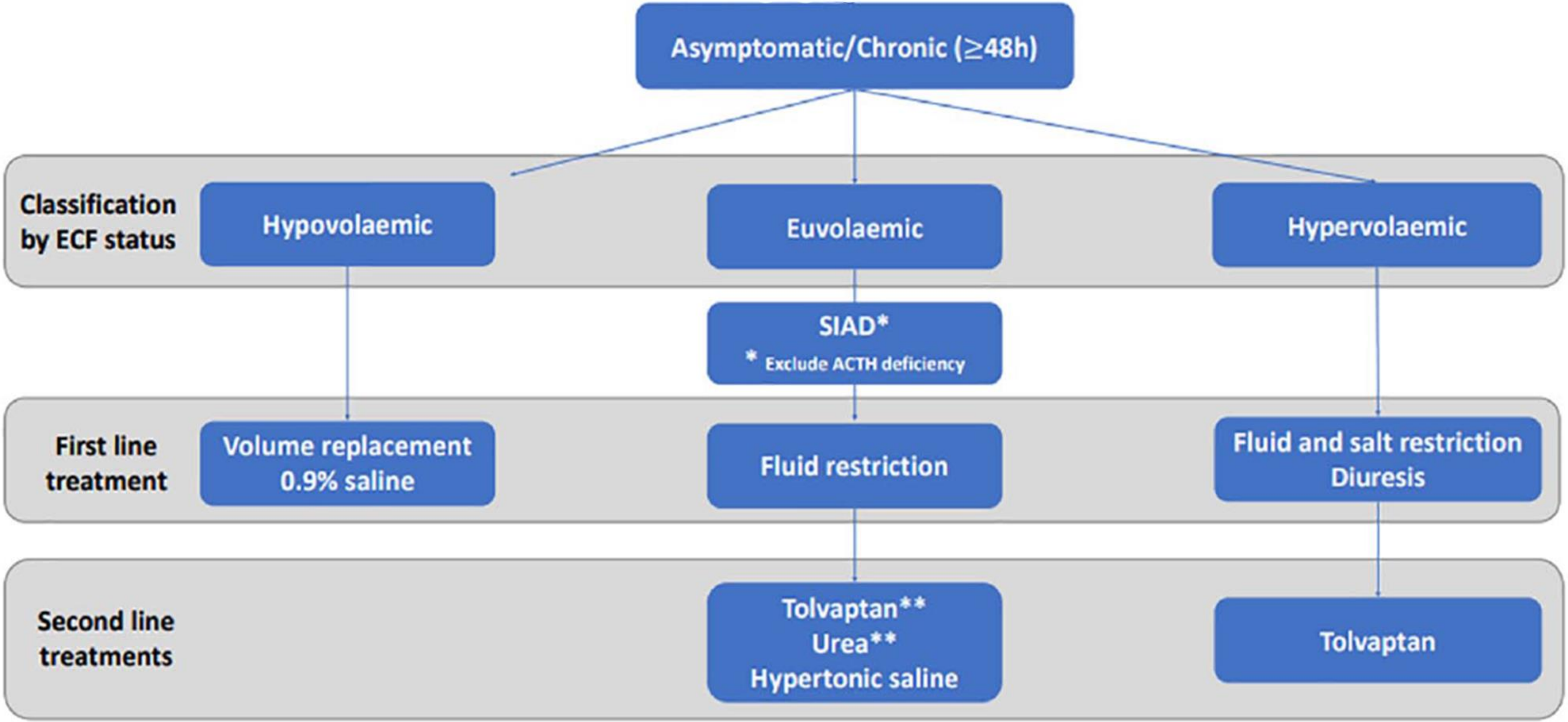
urea therapy (46 ± 25 g/day)

$P < 0.001$

135 ± 4 mEq/L

128 ± 4 mEq/L

Figure 1 Evolution of SNa and blood urea in 50 patients before and after urea therapy.



Asymptomatic/Chronic (≥48h)

Classification by ECF status

Hypovolaemic

Euvolaemic

Hypervolaemic

SIAD*

* Exclude ACTH deficiency

First line treatment

Volume replacement 0.9% saline

Fluid restriction

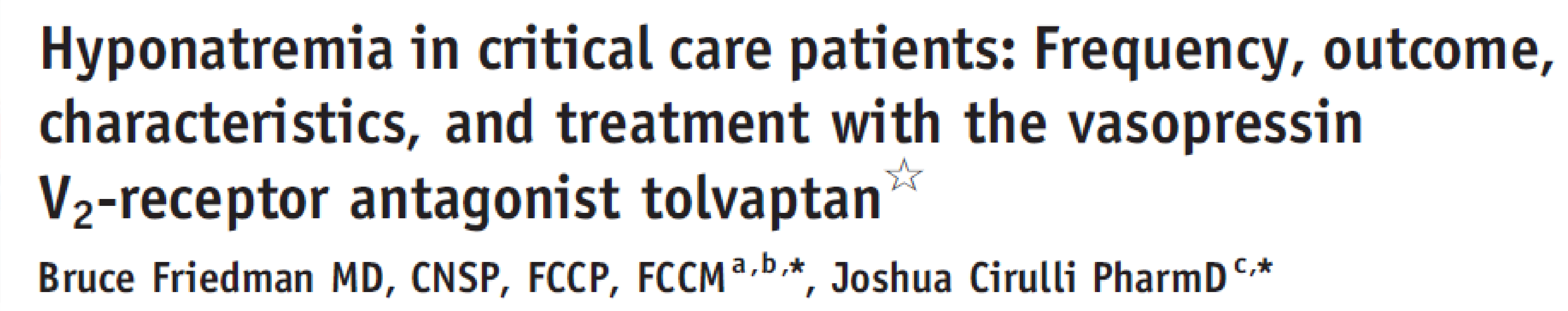
Fluid and salt restriction
Diuresis

Second line treatments

Tolvaptan**
Urea**
Hypertonic saline

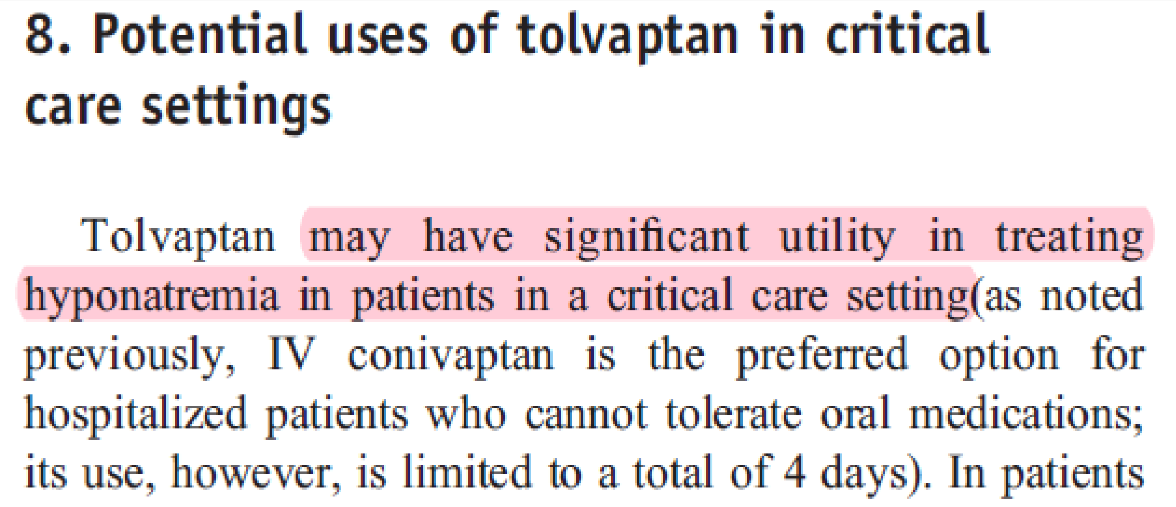
Tolvaptan

Ther Adv Endocrinol Metab 2022, Vol. 13: 1–16



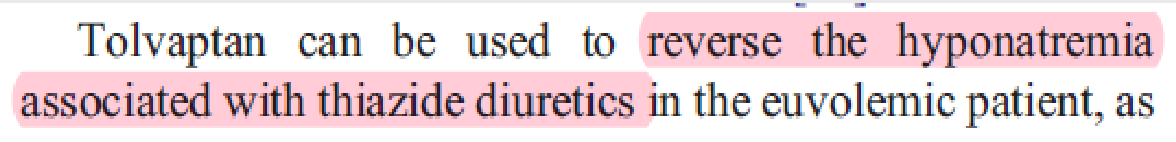
Hyponatremia in critical care patients: Frequency, outcome, characteristics, and treatment with the vasopressin V_2-receptor antagonist tolvaptan☆

Bruce Friedman MD, CNSP, FCCP, FCCM[a,b,*], Joshua Cirulli PharmD[c,*]

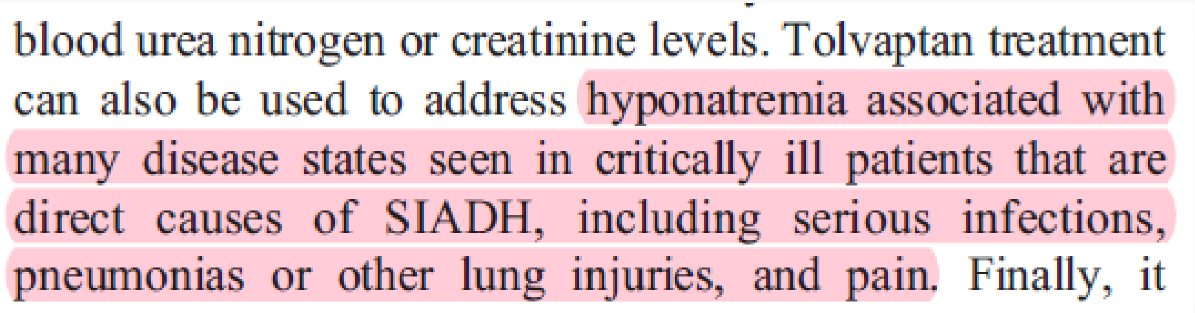


8. Potential uses of tolvaptan in critical care settings

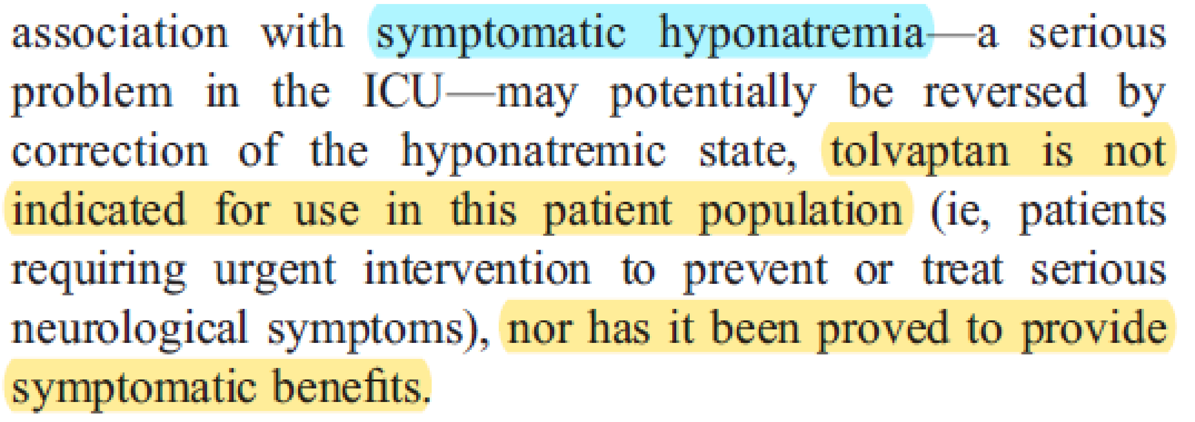
Tolvaptan may have significant utility in treating hyponatremia in patients in a critical care setting(as noted previously, IV conivaptan is the preferred option for hospitalized patients who cannot tolerate oral medications; its use, however, is limited to a total of 4 days). In patients



Tolvaptan can be used to reverse the hyponatremia associated with thiazide diuretics in the euvolemic patient, as



blood urea nitrogen or creatinine levels. Tolvaptan treatment can also be used to address hyponatremia associated with many disease states seen in critically ill patients that are direct causes of SIADH, including serious infections, pneumonias or other lung injuries, and pain. Finally, it



association with symptomatic hyponatremia—a serious problem in the ICU—may potentially be reversed by correction of the hyponatremic state, tolvaptan is not indicated for use in this patient population (ie, patients requiring urgent intervention to prevent or treat serious neurological symptoms), nor has it been proved to provide symptomatic benefits.

Journal of Critical Care (2013) **28**, 219.e1–219.e12

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Faut-il traiter toutes les hyponatrémies en réanimation ?

- OUI
- Lourde morbi-mortalité
- Hyponatrémie symptomatique : SSH 3% (recommandations américaine ou européenne)
- Hyponatrémie asymptomatique : traitement étiologique, restriction hydrique, urée? Tolvaptan?